FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

CHANGES OF HARM PERCEPTION AND EFFECT OF HEALTH WARNINGS ON ELECTRONIC CIGARETTE USE IN US YOUTH

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by

Wei Li

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To: Dean Tomás R. Guilarte
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This dissertation, written by Wei Li, and entitled Changes of Harm Perception and Effect of Health Warnings on Electronic Cigarette Use in US Youth, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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Florida International University, 2022

DEDICATION

This dissertation is dedicated to my family, friends and people who have provided me the kind of help that I need. Thank you for supporting me throughout my education and making me see this adventure through to the end.

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ABSTRACT OF THE DISSERTATION

CHANGES OF HARM PERCEPTION AND EFFECT OF HEALTH WARNINGS ON ELECTRONIC CIGARETTE USE IN US YOUTH

by

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Florida International University, 2022

Miami, Florida

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This dissertation 1) assessed the influence of electronic nicotine delivery systems (ENDS) harm perception on ENDS initiation over time among US youth and young adults; 2) tracked the changes in harm perception of ENDS use and examined their predictors among US youth; 3) conducted a pilot study to address the effectiveness of graphic health warning labels (GHWLs) on important outcomes among US young adult ENDS users. Data from 2013-2018 of the Population Assessment of Tobacco and Health (PATH) study were used for aims 1 & 2. Primary data with 26 participants that were collected from university campus during the year 2019 were used for aim 3.

In the first study, 17.1% of adolescents and 25.5% of young adults who never used ENDS at Wave 1, initiated ENDS use in subsequent waves. Perceiving ENDS as lower relative harm predicted ENDS initiation among adolescents (HR=2.33; 95%CI: 1.98-2.74) and young adults (HR=2.01; 95%CI: 1.72-2.36). Perceiving ENDS as lower absolute harm (HR=2.22; 95%CI: 1.87-2.63) predicted ENDS initiation among adolescents.

In the second study, adolescents who perceived ENDS as lower relative and absolute harm significantly decreased between Wave 1 and Wave 4 (P's<0.001). These changes in ENDS harm perception were less noticeable among males, those who had negative tobacco-related attitudes, and those with smoke-free home rules (P's<0.05). Having ever used ENDS/alcohol was more likely associated with reduced ENDS-related harm perception over time (P's<0.05).

The final study evaluated the effect of placing GHWLs on the ENDS devices on users' experience. Compared to the control sessions, using JUUL with GHWLs on the device was significantly associated with reduced positive experience such as pleasure, and product liking (P's<0.05). Also, after exposure to GHWLs, participants were less interested in using the same product again (P=0.01), even if it was the only ENDS product available on the market (P=0.03).

This study highlighted the importance of harm perception for ENDS initiation and the central role of risk communication strategies that need to target young people at risk of unwarranted ENDS use. Additionally, this proposal emphasized the demand for more effective tobacco regulatory policies to deter the ENDS epidemic among young people.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

ACASI	Audio computer-assisted self-interviews
AHP	Absolute harm perception
BMI	Body mass index
CAPI	Computer-assisted personal interviewing
CDC	Center for Disease Control and Prevention
CHP	Comparative harm perception
CI	Confidence interval
COVID-19	Coronavirus disease 2019
ENDS	Electronic nicotine delivery systems
FDA	US Food and Drug Administration
GC-MS	Gas chromatography-mass spectrometry
GHWL	Graphic health warning label
HAVE	Host, Agent, Vector, Environment model
HR	Hazard ratio
HWL	Health warning label
LOQ	Limit of quantitation
OR	Odds ratio
PATH	Population Assessment of Tobacco and Health
RHP	Relative harm perception
SD	Standard deviation
TVEM	Time-varying effect model
VAS	Visual Analog Scal

INTRODUCTION

The use of electronic nicotine delivery systems (ENDS; e-cigarettes) has exponentially increased and reached an epidemic level in the United States (US), particularly among young people (Gentzke et al., 2020; Park-Lee et al., 2021). Among young adults (18-24 years), the current use of ENDS (past 30-day use) increased from 2.4% in 2012 to 9.3% in 2019 (Agaku et al., 2014; Cornelius et al., 2020). Although the current ENDS use went down from 2020 to 2021 among middle school (4.7% to 2.8%) and high school (19.6% to 11.3%) students (Cullen et al., 2019; Park-Lee et al., 2021), the US Food and Drug Administration (FDA) maintains that ENDS use is still a serious public health concern amid the COVID-19 pandemic, with over 2 million US middle and high school students reporting current use of ENDS in 2021 (US Food & Drug Administration, 2021).

The rapid growth in ENDS has triggered interest in tobacco harm reduction, suggesting that ENDS are less harmful than combustible tobacco products (Chen et al., 2017) and could help reduce the use of combustible cigarettes by encouraging cessation or switching to ENDS (Abrams et al., 2018). Although the long-term health effects of ENDS use are still unclear, accumulating evidence suggests that ENDS are not harmless (Yuan et al., 2015; US Department of Health and Human Services, 2016; Vogel et al., 2018; Watkins et al., 2018; O'Brien et al., 2021). For example, literature shows that ENDS contain nicotine, which can lead to nicotine dependence/addiction (Vogel et al., 2018) and impaired brain development (Yuan et al., 2015; US Department of Health and Human Services, 2016). Moreover, ENDS use is associated with an increased risk of subsequent smoking initiation (O'Brien et al., 2021) and dual-use of tobacco products

(Watkins et al., 2018). Therefore, it is essential for studies to examine the factors that drive ENDS use in the general population, particularly with respect to ENDS initiation among young people.

To date, ENDS use among young people has been found to be associated with various factors that are known to affect the use of tobacco products among this population in general, such as friends, family influences, advertising, other tobacco products, and substance use (Bold et al., 2017; Hartwell et al., 2017; Amin et al., 2020). However, ENDS-specific product attributes appear to attract youth to try and use the products. For example, a review study found that the most cited reasons for ENDS uptakes among youth were curiosity, flavors, cost, and reduced harm perception compared to other tobacco products (Sapru et al., 2020). Specifically, harm reduction claims surrounding ENDS can push young nonsmokers to try these products (Klein et al., 2016). Harm perception is an important predictor of tobacco use behavior and can impact transitions between tobacco products (Hammig et al., 2017; Pepper et al., 2017; Persoskie et al., 2019). The 2014 US National Youth Tobacco Survey observed that perceiving ENDS as "little to no harm" or "less addictive than cigarettes" was associated with a higher likelihood of ENDS initiation among youth (Hammig et al., 2017).

However, little is known about how harm perception has changed over time, its predictors, and whether the changes affect ENDS initiation at the population level. Using the Population Assessment of Tobacco and Health (PATH) study with four waves from 2013-2018, the first two studies seek to: 1) assess the influence of relative and absolute harm perception on ENDS initiation among adolescents and young adults; and 2) characterize changes in ENDS-related harm perception at the population level and their

predictors over time. These findings will provide a comparative overview of the real-world evolution of harm perception on ENDS use at the population level and suggest potentially effective avenues for research and policy to reduce ENDS use among young people in the future.

Communicating risks associated with ENDS use has been identified as a top priority to reduce ENDS use among young people in the US (Center for Diseases Control and Prevention, 2020). Health warning labels (HWLs) have emerged as an important medium for communicating the harms of tobacco use to the public. However, only text warning about nicotine addiction is currently mandated on ENDS packages, which opens the door for exploring potentially more effective options such as applying graphic health warning labels (GHWLs) on the device itself. In cigarette literature, studies have consistently demonstrated that GHWLs are associated with a decrease in smoking rates, smoking-related morbidity, and mortality (Huang et al., 2014; Noar et al., 2016; Green et al., 2016) and diminished smoking subjective experience (e.g., willingness and intention to smoke) (Schneider et al., 2012; Blanton et al., 2014; Evans et al., 2015). To date, no study has been conducted to assess the effectiveness of GHWLs during ENDS use on a variety of regulatory important outcomes (e.g., harm perception, intention to quit). Therefore, the third study from this dissertation will further test a promising strategy to communicate and affect risk/harm perception among young ENDS users, providing a proof of concept that placing GHWLs on the ENDS devices is an effective means of communicating health risks of ENDS use to young users.

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MANUSCRIPT 1

Effect of Harm Perception on ENDS Initiation among US Adolescents and Young Adults: Findings from the Population Assessment of Tobacco and Health (PATH) Study, 2013-2018

Abstract

Background: Electronic Nicotine Delivery Systems (ENDS) have become the most popular tobacco products among youth in the United States (US). This study aims to investigate how ENDS harm perception predicts ENDS initiation among never ENDS users.

Methods: Data were from the youth and adult sample of the Population Assessment of Tobacco and Health (PATH) study conducted from 2013-2018. Cox proportional hazards regression models were used to assess the relationship between harm perception and ENDS initiation among adolescents and young adults separately. Weighted adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

Results: Of the 11,633 adolescents and 5,089 young adults from baseline, 17.1% and 25.5% initiated ENDS use across four waves, respectively. Among adolescents (HR=2.33; 95%CI: 1.98-2.74) and young adults (HR=2.01; 95%CI: 1.72-2.36), perceiving ENDS as less harmful than cigarettes significantly predicted ENDS initiation in subsequent waves. Among adolescents, perceiving ENDS as no or little harm (HR=2.22; 95%CI: 1.87-2.63) predicted ENDS initiation in subsequent waves. Additionally, adolescents and young adults who ever used any other tobacco products or alcohol and lived with anyone who used tobacco were more likely to initiate ENDS use.

Conclusions: Among a representative longitudinal cohort of adolescents and young adults who had never used ENDS from baseline, perceiving ENDS as reduced or low-harm products significantly predicted ENDS initiation in subsequent waves. These findings underscore the importance of ENDS harm perception, and the central role of risk communication strategies that need to target those young people who are at particular risk of unwarranted ENDS use.

Keywords: ENDS initiation, e-cigarette, harm perception, tobacco control, young people

Introduction

Tobacco use is a global concern, especially among young people (US Department of Health and Human Services, 2016). As of 2014, Electronic Nicotine Delivery Systems (ENDS), also known as electronic cigarettes or e-cigarettes, have become the most popular tobacco products among youth in the United States (US) (Park-Lee et al., 2021). Among young adults (18-24 years), the current use of ENDS (past 30-day use) increased from 2.4% in 2012 to 9.3% in 2019 (Agaku et al., 2014; Cornelius et al., 2020). Although the current use of ENDS decreased from 2019 to 2021 among middle school (10.5% to 2.8%) and high school (27.5% to 11.3%) students amid the Coronavirus Disease 2019 (COVID-19) pandemic (Cullen et al., 2019; Park-Lee et al., 2021), the US Food and Drug Administration (FDA) maintains that ENDS use is still a serious public health concern, with over 2 million US middle and high school students reporting current use of ENDS in 2021 (US Food & Drug Administration, 2021).

The rapid growth in ENDS use has triggered interest in tobacco harm reduction, suggesting that ENDS could help reduce the use of combustible cigarettes by encouraging cessation or switching to ENDS (Abrams et al., 2018). Clinical trials suggest

that ENDS may help smokers quit smoking, although the long-term side effects of ENDS use are still unknown (Zhu et al., 2017; Hartmann-Boyce et al., 2020; Hajek et al.,2019). Of particular concern is ENDS risk for youth who are mostly outside the harm reduction focus on adult smokers interested in quitting. Growing evidence suggests that ENDS use in youth is linked to nicotine addiction/dependence (Vogel et al., 2018) and impaired brain development (Yuan et al., 2015; US Department of Health and Human Services, 2016). Moreover, ENDS use is associated with an increased risk of subsequent smoking initiation (O'Brien et al., 2021) and dual-use of tobacco products (Watkins et al., 2018).

To date, ENDS use among young people has been found to be associated with various factors that are known to affect the use of tobacco products among this population in general, such as friends, family influences, advertising, other tobacco products, and substance use (Bold et al., 2017; Hartwell et al., 2017; Amin et al., 2020). However, ENDS-specific product attributes appear to attract youth to try and use the products. For example, a review study found that the most cited reasons for ENDS uptakes among youth were curiosity, flavors, cost, and reduced harm perception compared to other tobacco products (Sapru et al., 2020). Specifically, harm reduction claims surrounding ENDS can push young nonsmokers to try these products (Klein et al., 2016). Harm perception is an important predictor of tobacco use behavior and can impact transitions between tobacco products (Pepper et al., 2017; Hammig et al., 2017; Persoskie et al., 2019). The 2014 US National Youth Tobacco Survey observed that perceiving ENDS as "little to no harm" or "less addictive than cigarettes" was associated with a higher likelihood of ENDS initiation among youth (Hammig et al., 2017).

Longitudinal studies are needed to look at the role of harm perception in driving ENDS initiation among youth (Choi and Forster, 2014; Brose et al., 2015; Cooper et al., 2018). Cooper et al. found that perceiving ENDS as low harm predicted the initiation among young adult nonsmokers in Texas colleges during a 2-year follow-up (Cooper et al., 2018). Among British adults, Brose et al. showed that perceiving ENDS as less harmful than cigarettes predicted subsequent ENDS use over two years (Brose et al., 2015). However, as the ENDS epidemic among US youth is of a national proportion and their perception of harm is ever-changing (Li et al., 2022), longitudinal studies looking at this relationship in national samples of young people are still needed. Such studies can provide a dynamic picture of how harm perception influences ENDS use among young people in society over time and whether investing in harm awareness strategies among youth is a promising avenue for public health. In this study, we used four waves (2013-2018) of the Population Assessment of Tobacco and Health (PATH) study to examine the effect of harm perception on ENDS initiation among US adolescents and young adults over a four-year period.

Methods

Study Design and Population

Data are from baseline and three follow-up waves of the PATH Study conducted between September 2013 and January 2018. The PATH Study is an ongoing, longitudinal cohort survey of 45,971 adolescents and adults to explore how tobacco use affects people's health in the US (Hyland et al., 2017). The study used computer-assisted personal interviewing (CAPI) and audio computer-assisted self-interviewing (ACASI) to collect information on tobacco-use patterns and associated health behaviors among

adolescents and adults separately (Hyland et al., 2017). Adult participants provided informed consent, and adolescents aged 12 to 17 were interviewed with parental permission. Weighted procedures were used to compensate for different probabilities of selection, nonresponse, and oversampling of adult tobacco users, young adults (18-24 years), and non-Hispanic African American adults. Further details of the PATH Study and Westat Institutional Review Board-approved protocols can be found elsewhere (Hyland et al., 2017). This current study focused on investigating the influence of relative and absolute harm perception on ENDS initiation among adolescents (12-17 years) and young adults (18-24 years) who never used ENDS at baseline (Wave 1).

Study Measures

Outcome

ENDS initiation was defined as change from never use of ENDS at Wave 1 to ever use of ENDS at any subsequent wave (waves 2-4), based on definitions from past literature on smoking initiation (Hammond et al., 2017). All adult and adolescent participants were asked, "Have you ever used an electronic nicotine product, even one or two times?" Those who responded "Yes" were operationalized as ever use of ENDS.

Exposure

In PATH, harm perception of tobacco products is measured in two ways, relative and absolute harm perception (Wackowski et al., 2016; Parker et al., 2018).

Relative harm perception (RHP) was assessed by the question among adults and adolescents, "Is using ENDS less harmful, about the same, or more harmful than smoking cigarettes?" Based on previous research (Malt et al., 2020), we categorized the responses as less harmful vs. same or more harmful than cigarettes (reference group).

Absolute harm perception (AHP) was dichotomized as no or little harm vs. some or a lot of harm (reference group) according to the similar classification from RHP (Malt et al., 2020), by asking, "How much do you think people harm themselves when they use ENDS?" The original responses were: 1) no harm; 2) little harm; 3) some harm; and 4) a lot of harm.

Covariates

Covariates of interest were selected based on previous literature regarding the relationship between harm perception and ENDS initiation (Choi and Forster, 2014; Brose et al., 2015; Tan et al., 2016; Czoli et al., 2017; Cooper et al., 2018) and the theoretical framework of the PATH Study (Hyland et al., 2017). Specifically, the PATH Study is based on the Host, Agent, Vector, Environment (HAVE) model and how their interactions influence health and behavioral outcomes (Hyland et al., 2017). Host factors refer to individuals who are at risk of becoming tobacco users, including demographics, tobacco-related attitudes, health status, and risk behaviors in the present study. Agent factors are related to the tobacco products' packaging, formulation, design, and promotions, including exposure to health warnings and media use in this study. Environmental factors encompass current policies, social, cultural, and geographic influences, including family/peer influence, smoke-free home rules, and parents' education. The vector facilitates interactions between host, agent, and environments.

Host factors:

Demographic variables included age (for adolescents: 12-14 years, 15-17 years; for young adults: 18-24 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic other), gender (male, female), region (northeast, Mideast, south,

west), education (for adolescents: 6-8 grade, 9-12 grade; for young adults: less than high school, high school, some college, and advanced degree), income for adolescents (money received per week: $0, $1-$20, >$20) and poverty for adults (below poverty level vs. at or above poverty level).

Tobacco-related attitudes: For adolescent, they were asked by six questions, "1. I think I would enjoy using tobacco; 2. Using tobacco would be energizing; 3. Using tobacco would help me reduce or handle stress; 4. Using tobacco would help me calm down when I am angry; 5. Using tobacco would help me control my weight; 6. Using tobacco would help me feel more comfortable at parties". The participants were considered as having a positive attitude towards tobacco if they agreed with any of above questions. Young adults were asked by, "How would you describe your overall opinion of tobacco?" and the answers were recoded as positive/neutral and negative.

Health status included overall health, mental health, and physical health.

- *Overall health* was evaluated by, "In general, would you say your overall health is excellent, very good, good, fair, and poor?" among all adolescents and young adults.

- *Mental health* and *physical health* were only available in the adult dataset. Respectively, the questions were: “In general, how would you rate your mental health, which includes stress, depression, and problems with emotions?” and “In general, how would you rate your physical health?” with answers, “excellent, very good, good, fair and poor”. The responses were all treated as three categories: excellent/very good, good, and fair/poor. Since only a few participants responded fair and poor, we coded them together as one category.

Risk behaviors included other tobacco products use, substance use, susceptibility to ENDS use, and sensation seeking.

- *Tobacco products use* included cigarette use and other tobacco products use. All adolescent and young adult participants were asked: "Have you ever used cigarette or other tobacco products (cigars, smokeless tobacco, traditional cigars, filtered cigars, pipe tobacco, snus pouches, dissolvable tobacco, bids, kreteks, hookah or cigarillos)?"

- *Substance use* included drug use and alcohol use. All adolescent and young adults were asked: "Have you ever used any substance (marijuana, prescription drugs, cocaine or crack, stimulants, heroin, inhalants, solvents, and hallucinogens) or alcohol?"

- Only adolescents were asked about susceptibility to ENDS use and sensation seeking. Specifically, for *susceptibility to ENDS use*, three items were assessed (Seo et al., 2020), and the response options for each item (1=definitely not, 2=probably not, 3=probably yes, 4=definitely yes) were summed to create mean and overall (range: 3–12) scores. The three questions were: "1. Ever been curious about using ENDS; 2. Think you will try an ENDS soon; 3. Would use an ENDS if one of your best friends offered you one".

- For *sensation seeking*, three items were assessed, and the response options for each item (1=strongly disagree, 2=disagree, 3=neutral, 4=agree, 5=strongly agree) were summed to create mean and overall (range: 3–15) scores (Conway et al., 2018) by asking three questions, "1. Like to do frightening things; 2. Like new and exciting experience, even if I have to break the rules; 3. Prefer friends who are exciting and

unpredictable". Higher scores reflect higher susceptibility to ENDS use and sensation seeking.

Agent factors:

Parents' education was only asked among adolescents and categorized into four levels, which is similar as the categories for adults.

Media use: Adolescent and adults were asked whether they ever accessed to online sources about tobacco products (e.g., sign up for email alerts, read articles, or watch a video online) during the past 6 months.

Exposure to health warning was assessed by asking whether they have ever noticed the health warnings on packages of cigarettes and ENDS.

Environmental factors:

Smoke-free home rules were measured among both adolescents and adults by asking whether they were allowed to use any tobacco product inside the homes.

Family/peer influence was assessed using the question, "Does anyone who lives with you use any form of tobacco product?" for both adolescent and adult participants.

Statistical Analysis

Statistical analysis was conducted in the following steps. First, two longitudinal datasets were created regarding ENDS initiation among adolescents (n=11,633) and young adults (n=5,089) who never used ENDS from baseline. Second, a programming statement method was applied to incorporate time-dependent variables (all the variables presented in table 1 except gender, race, region, and parents' education) measured from waves 1-3 in the regression analyses (Powell and Bagnell, 2012). This method generated only one record for each participant, corresponding to when initiation occurred (Allison,

2010). Third, descriptive statistics for the study sample's basic characteristics were reported as means and standard deviations for continuous variables or frequencies for categorical variables. Fourth, since some questions were asked only at baseline such as weekly income, media, smoke-free home rules, tobacco-related attitudes, and sensation-seeking, we only measured these variables from Wave 1. Fifth, the Cox proportional hazards regression models were used to evaluate the hazard ratios (HRs) of ENDS initiation (Powell and Bagnell, 2012). Harm perception and other covariates were selected from a previous wave to predict ENDS initiation at the current wave. Further, single wave 1 weight and all-wave replicate weights were applied for descriptive statistics and survival models, respectively. Last, a sensitivity analysis was conducted and restricted to those who had complete data when the replicate weight was applied. Since the significant findings and directions of the base model did not differ from the sensitivity analyses, the unadjusted and adjusted HRs with 95% confidence intervals (CIs) from the previous analyses were reported. All analyses were conducted in SAS (Statistical Analysis System Institute, Cary, NC, US, version 9.4), and a two-sided p-value < 0.05 was considered as statistically significance.

Results

Sample characteristics

Adolescents

Among 11,663 adolescents who never used ENDS at baseline (**Table 1**), 17.1% of them initiated ENDS use from Wave 2 to Wave 4. Around half of the ENDS initiators (50.5%) were males. More than half of the initiators identified as non-Hispanic White (58.8%) or between 12-14 years (61.7%). Those who reported ENDS as less harmful than

cigarettes had a higher proportion of ENDS initiation in the subsequent waves compared to those who reported ENDS as the same as or more harmful than cigarettes (**Figure 1A**). Similar results were noticed between absolute harm perception and ENDS initiation (**Figure 1B**). In total, 58.7% of the adolescent initiators reported ENDS as less harmful than cigarettes, and 40.4% reported ENDS as no or little harm from Wave 1 to Wave 3.

Young adults

Among 5,089 young adults who never used ENDS at baseline (**Table 1**), 25.5% initiated ENDS use in the following waves. Around half of the initiators (49.5%) were males, and 47.5% were non-Hispanic Whites. Those who reported ENDS as less harmful than cigarettes had a higher proportion of ENDS initiation in the subsequent waves compared to those who reported ENDS as the same as or more harmful than cigarettes (**Figure 1C**). In total, 48.4% of the initiators reported ENDS as less harmful than cigarettes from Wave 1 to Wave 3. More detailed information about the descriptive characteristics is presented in **Table 1** and **Figure 1**.

Harm perception and ENDS initiation

Adolescents

Adjusted models showed that compared to the respective reference groups, perceiving ENDS as less harmful than cigarettes (HR=2.33; 95%CI: 1.98-2.74) and ENDS as no or little harm (HR=2.22; 95%CI: 1.87-2.63) significantly increased risks of ENDS initiation in subsequent waves among adolescents (**Table 2**). Additionally, younger age (12-14 years) was associated with an increased risk of ENDS initiation (RHP: HR=2.59; 95%CI: 2.17-3.10; AHP: HR=2.55; 95%CI: 2.17-2.99). Moreover, living with anyone who used tobacco predicted ENDS initiation in subsequent waves

(RHP: HR=1.28; 95%CI: 1.05-1.56; AHP: HR=1.24; 95%CI: 1.02-1.50). Other tobacco products and alcohol use significantly predicted ENDS initiation in the subsequent waves. For example, adolescents who ever used other tobacco products were more likely to initiate ENDS use in the subsequent waves (RHP: HR=1.62; 95%CI: 1.13-2.33; AHP: HR=1.56; 95%CI: 1.07-2.27). Furthermore, higher sensation-seeking (RHP: HR=1.11; 95%CI: 1.08-1.15; AHP: HR=1.11; 95%CI: 1.08-1.14) and susceptibility to ENDS use (RHP: HR=1.25; 95%CI: 1.19-1.32; AHP: HR=1.20; 95%CI: 1.15-1.28) scores were associated with a higher risk of ENDS initiation.

Young adults

Among young adults (**Table 3**), the adjusted model indicated that perceiving ENDS as less harmful than cigarettes was associated with an increased risk of ENDS initiation (HR=2.01; 95%CI: 1.72-2.36) in subsequent waves compared to perceiving ENDS as the same as or more harmful than cigarettes. Young adults who held positive attitudes toward tobacco products (HR=1.53; 95%CI: 1.29-1.81) and lived with anyone who used tobacco (HR=1.27; 95%CI: 1.08-1.50) had an increased risk of ENDS initiation. Moreover, young adults who ever used cigarettes (HR=2.60; 95%CI: 1.94-3.48), other tobacco products (HR=2.55; 95%CI: 1.91-3.40), drugs (HR=2.59; 95%CI: 2.20-3.07) or alcohol (HR=1.65; 95%CI: 1.29-2.11) were more likely to initiate ENDS use in the subsequent waves.

Discussion

This study examined the influence of relative and absolute harm perception on ENDS initiation among adolescents and young adults in a real-world setting using a unique population-based longitudinal dataset. Overall, 17.1% of the adolescents and

25.5% of the young adults initiated ENDS use across the four waves. The perception of ENDS as a reduced or low-harm product strongly predicted ENDS initiation in the subsequent waves among US young people. Additionally, adolescents and young adults who experimented with other tobacco products or alcohol and lived with anyone who used tobacco were at increased risks of ENDS initiation. Characterizing the role of harm perception in ENDS initiation in a real-world setting can help inform risk communication strategies to reduce unwarranted ENDS uptakes among young people.

Our study highlights the importance of harm perception for ENDS initiation among young people. The tobacco harm reduction approach aims to encourage those who are unable to quit smoking to reduce their harm by switching to ENDS (National Institute of Health and Care Excellence, 2013). Randomized control trials support the potential benefits of ENDS to adult smokers (Hajek et al., 2019; Hartmann-Boyce et al., 2020; Rigotti, 2020), yet population based real-world studies have shown the opposite (Watkins et al., 2018; Dai and Leventhal, 2019). Although evidence informing such debate continues to accumulate, the central role of reduced harm of ENDS has been their marketing cornerstone, mostly through youth oriented social media (Klein et al., 2016; Sapru et al., 2020). While such promotion can be beneficial to adult smokers who desperately want to reduce their harm, our study shows that it is likely affecting tobacco-naïve adolescents, especially for whom cessation or harm reduction is not a main reason for ENDS use (Cooper et al., 2018). As this study shows perceiving ENDS as reduced or low-harm products predicted ENDS initiation over time among adolescents, 14.9% and 7.3% of whom ever used cigarettes and other tobacco products, respectively. Subsequently, limiting that marketing within smoking cessation services settings can

preserve the potential benefits of ENDS, while protecting young users from getting into lifelong nicotine addiction. This is particularly important as increasingly evidence is showing that young people starting with ENDS use are more likely to initiate cigarette smoking later (O'Brien et al., 2021; Watkins et al., 2018).

Susceptibility to tobacco use is a strong predictor of tobacco initiation and use (Cheng et al., 2021). In this study, we assessed susceptibility to ENDS use and sensation-seeking by using a cumulative score and found that a higher score predicted a higher likelihood of ENDS initiation among adolescents. A previous study conducted in a rural county from Tennessee state demonstrated that the susceptibility to ENDS use was significantly associated with ever use of ENDS (Mamudu et al., 2020). Another study conducted among Texas adolescents found that a higher sensation seeking score was significantly and consistently related to experimentation with ENDS use (Case et al., 2017). These findings are important for guiding future strategies (e.g., communication campaigns) that are effective for targeting susceptible adolescents and sensation seekers in preventing ENDS uptakes.

Similar to existing literature (Amin et al., 2020; Cavazos-Rehg et al., 2021), our findings underscore the vital role of peer and social influence on ENDS use-that is living with anyone who used tobacco was significantly associated with an increased risk of ENDS initiation. Previous literature showed that parental reactions and friend tobacco use significantly impact ENDS initiation and persistence use (Cavazos-Rehg et al., 2021). Although we only used one question to assess the relationship between peer influence and ENDS initiation, the results from this study correspond with the previous literature suggest significant implications for adolescent behaviors following the emergency of

novel tobacco products use. For the sake of limited evidence in ENDS long-term health effects, parental and peer influences may closely be relevant for contributing to their initiation and popularity among adolescents.

Limitations and strengths

Several limitations involved in this study need to be noted. First, the harm perception of ENDS use was evaluated via a general question, which may not capture specific domains of harms related to ENDS use (e.g., toxicants in e-liquid, aerosol constituents, and health effects). Second, as mentioned in the methods section, we attempted to incorporate all the covariates as time-dependent variables. Unfortunately, some questions were only asked at the baseline (e.g., media, weekly income, smoke-free home rules, etc.). This may not reflect how these variables affect the outcome across time. Further, because more than 80% of the ENDS-specific health warning responses were missing, we combined the ENDS and cigarette health warning questions. Therefore, the question involved in this study may not capture the true effects of ENDS-specific health warnings on ENDS initiation. Future research is warranted to investigate the potential influence of ENDS-specific health warnings on ENDS use at both individual and population levels. Despite these limitations, using a nationally representative sample in a real-world setting allows us to examine the influence of absolute and relative harm perception on ENDS use among adolescents and young adults in an extended period. In this respect, the findings from this study are consequential in guiding tailored interventions through risk communication to benefit from ENDS as smoking cessation tools without encouraging tobacco-naïve users' uptakes.

Conclusions

Perceiving ENDS as reduced or low harm products significantly predicted ENDS initiation among a cohort of adolescents and young adults from the PATH Study. As marketing and promotion of these products shapes young people's harm perception and attitudes toward them, health communication strategies conveying information about their risk profile can be a promising strategy for intervention. However, such strategies should be applied with caution as to allow those who can benefit from ENDS to quit smoking or reduce their harms seek that option. Additionally, adolescents and young adults who ever used tobacco products or alcohol and lived with anyone who used tobacco were associated with increased risks of ENDS initiation. These findings not only extend existing research on the strong association of ENDS-specific harm perception on ENDS initiation with a long period, but also underscore the importance of ENDS harm perception, and the central role of risk communication strategies that need to target those young people who are at particular risk of unwarranted ENDS use. Further research is deserved to investigate how the specific domains of harms related to ENDS use may influence the transitions in stages of ENDS use behaviors and prevent future ENDS use among young generations.

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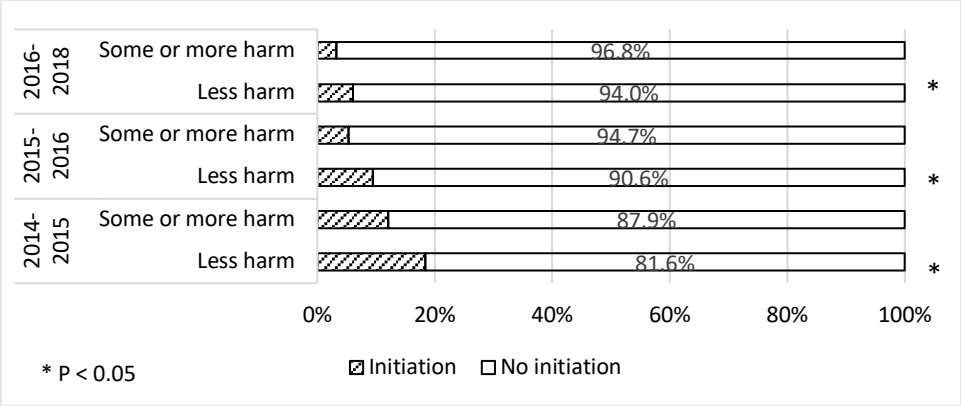
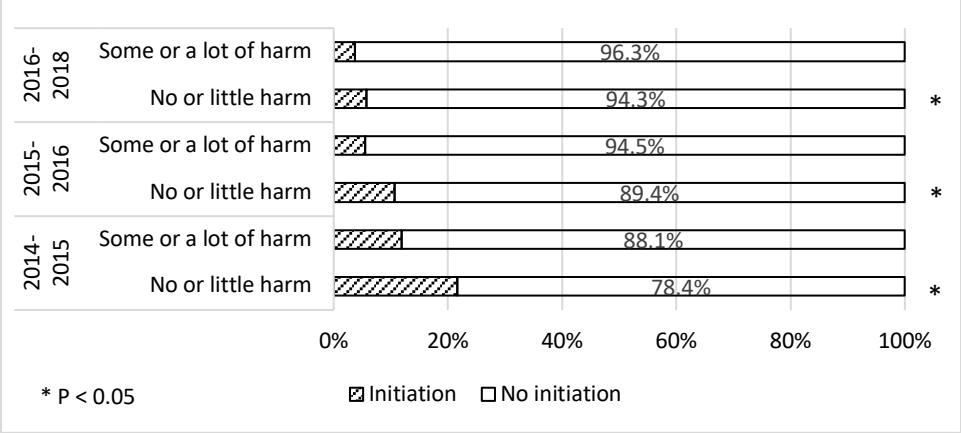
Figures and Tables

Figure 1. Relative harm perception of ENDS initiation among adolescents (12-17 years) (panel A); Absolute harm perception of ENDS initiation among adolescents (12-17 years) (panel B); Relative harm perception of ENDS initiation among young adults (18-24 years) (panel C): Population Assessment of Tobacco and Health Study, 2013-2018.

A



B



C

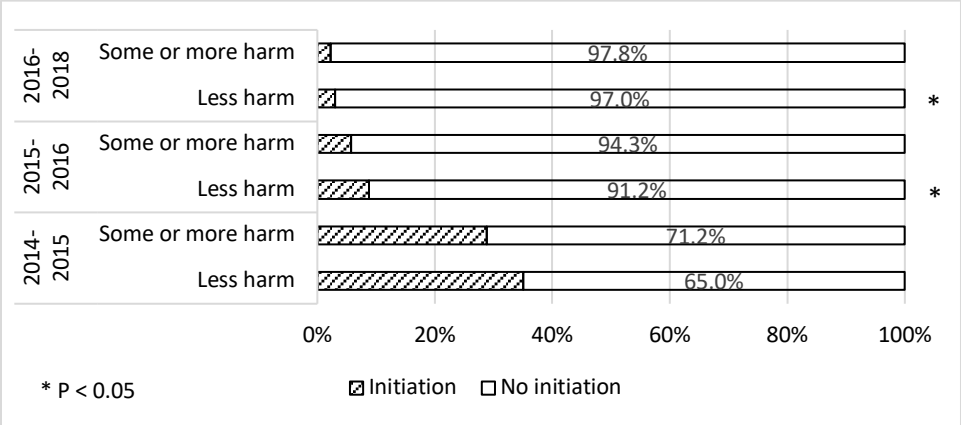


Table 1. Basic descriptive statistics for US adolescents (12-17 yrs) and young adults (18-24 yrs) ENDS initiation.

Variables	Adolescents ENDS initiation (N=11,633)		Young adults ENDS initiation (N=5,089)	
	Initiators*	**Non-initiators**	**Initiators***	**Non-initiators**
Total	1,989 (17.1)	9,644 (82.9)	1,595 (25.5)	3,494 (74.5)
Relative harm perception				
Less harmful	1,044 (58.7)	3,915 (49.5)	702 (48.4)	1,253 (40.0)
Same or more harmful	741 (41.3)	4,077 (50.5)	775 (51.6)	1,883 (60.0)
Absolute harm perception				
No or little harm	742 (40.4)	2,407 (27.7)	-	-
Some or a lot of harm	1,118 (59.6)	6,132 (72.3)	-	-
Gender (Male)	902 (50.8)	4,884 (50.5)	466 (49.5)	1,334 (43.8)
Race				
Non-Hispanic White	1,035 (58.8)	4,562 (53.3)	705 (47.5)	1,716 (53.9)
Non-Hispanic Black	193 (10.0)	1,454 (15.2)	298 (16.1)	666 (15.1)
Hispanic	583 (23.0)	2,756 (22.1)	457 (26.6)	778 (19.0)
Non-Hispanic Others	178 (8.2)	872 (9.5)	135 (9.8)	334 (12.1)
Region				
Northeast	326 (18.5)	1,431 (16.6)	254 (17.5)	537 (17.1)
Mideast	466 (23.2)	2,053 (21.3)	354 (19.3)	776 (20.9)
South	659 (33.9)	3,730 (38.0)	552 (35.6)	1,394 (38.8)
West	538 (24.4)	2,430 (24.0)	435 (27.7)	787 (23.2)
Education				
6-8 grade	870 (43.5)	4,007 (41.2)	-	-
9-12 grade	1,116 (56.5)	5,601 (58.8)	-	-
Less than high school	-	-	281 (15.3)	540 (13.0)
High school	-	-	494 (30.1)	1,033 (27.5)
Some college or college	-	-	681 (44.4)	1,408 (43.3)
Advanced degree	-	-	129 (10.2)	495 (16.2)

Income (weekly)/Poverty				
$0	639 (32.5)	3,303 (35.2)	-	-
$1-20	1,011 (51.2)	4,372 (45.3)	-	-
>$20	320 (16.3)	1,835 (19.5)	-	-
Below poverty level (< 100% of poverty guideline)	-	-	733 (48.4)	1,505 (45.3)
At or above poverty level (>= 100% of poverty guideline)	-	-	672 (51.6)	1,568 (54.7)
Ever used cigarettes (Yes)	298 (14.9)	547 (5.6)	987 (54.1)	1,299 (28.2)
Ever used other tobacco products (Yes)[†]	146 (7.3)	366 (3.8)	387 (21.9)	682 (14.8)
Ever used drug (Yes)[‡]	173 (9.4)	318 (3.4)	866 (49.2)	1,088 (24.1)
Ever used alcohol (Yes)	994 (50.8)	2,756 (29.5)	1,342 (83.0)	2,469 (68.8)

[*]Represents unweighted sample in numbers and weighted sample in percentage (%).
[†]Other tobacco products refer to cigars, smokeless tobacco, traditional cigars, filtered cigars, pipe tobacco, snus pouches, dissolvable tobacco, bids, kreteks, hookah or cigarillos.
[‡]Drug refers to marijuana, prescription drugs, cocaine or crack, stimulants, heroin, inhalants, solvents, and hallucinogens.
Note: numbers may not sum to the total due to missing data.

Table 2. Hazard ratios (HRs) of harm perception on ENDS initiation among adolescents (12-17 yrs).

Variables	ENDS initiation		
	Unadjusted HR* (95% CI)	**Adjusted HR for RHP# (95% CI)**	**Adjusted HR for AHP† (95% CI)**
Relative harm perception			
Same or more harmful	Ref.	Ref.	-
Less harmful	**3.28 (2.85-3.76)**	**2.33 (1.98-2.74)**	-
Absolute harm perception	Ref.	-	Ref.
Some or a lot of harm			
No or little harm	**3.95 (3.42-4.57)**	-	**2.22 (1.87-2.63)**
Age (yrs) (Ref.= 15-17)			
12-14	**3.67 (3.21-4.19)**	**2.59 (2.17-3.10)**	**2.55 (2.17-2.99)**
Gender (Ref.= male)			
Female	0.96 (0.85-1.10)	1.02 (0.88-1.19)	0.96 (0.83-1.11)
Race			
Non-Hispanic White	Ref.	Ref.	Ref.
Non-Hispanic Black	**0.53 (0.40-0.71)**	**0.51 (0.35-0.74)**	**0.50 (0.34-0.72)**
Hispanic	0.98 (0.82-1.16)	1.00 (0.80-1.24)	0.99 (0.80-1.24)
Non-Hispanic Others	**0.68 (0.52-0.89)**	**0.73 (0.56-0.96)**	**0.74 (0.57-0.98)**
Region			
Northeast	Ref.	Ref.	Ref.
Mideast	**0.79 (0.64-0.98)**	0.84 (0.66-1.06)	0.85 (0.66-1.10)
South	**0.65 (0.53-0.80)**	**0.74 (0.58-0.95)**	**0.72 (0.55-0.94)**
West	**0.75 (0.61-0.92)**	0.86 (0.68-1.09)	0.84 (0.65-1.09)
Education			
6-8 grade	Ref.	Ref.	Ref.
9-12 grade	**0.28 (0.25-0.32)**	**0.47 (0.40-0.57)**	**0.49 (0.41-0.58)**
Income (weekly)			
$0	Ref.	Ref.	Ref.
$1-20	**1.17 (1.03-1.34)**	1.06 (0.90-1.25)	1.10 (0.94-1.30)
>$20	**1.50 (1.19-1.87)**	**1.34 (1.03-1.73)**	1.29 (0.99-1.68)
Tobacco-related attitudes			
Negative	Ref.	Ref.	Ref.
Positive/Neutral	**2.66 (2.32-3.04)**	1.11 (0.90-1.37)	1.19 (0.96-1.47)
Media (Yes)	1.32 (0.98-1.76)	0.86 (0.60-1.24)	0.91 (0.63-1.33)
Anyone who lives with you now using tobacco (Yes)	**1.91 (1.63-2.23)**	**1.28 (1.05-1.56)**	**1.24 (1.02-1.50)**
Allowed to use tobacco inside home (Yes)	**1.93 (1.64-2.26)**	1.21 (0.99-1.48)	**1.23 (1.01-1.49)**
Health warning (Yes)	**1.54 (1.33-1.78)**	**1.19 (1.01-1.40)**	**1.18 (1.00-1.40)**
Parent education			

Less than high school	Ref.	Ref.	Ref.
High school	1.03 (0.83-1.28)	0.91 (0.65-1.27)	0.91 (0.66-1.25)
Some college or college	0.98 (0.82-1.19)	0.85 (0.64-1.12)	0.87 (0.66-1.16)
Advanced degree	**0.73 (0.57-0.94)**	**0.67 (0.46-0.97)**	0.69 (0.47-1.01)
Ever used cigarettes (Yes)	**3.20 (2.62-3.90)**	**1.48 (1.14-1.91)**	**1.41 (1.08-1.85)**
Ever used other tobacco (Yes) [†]	**2.35 (1.86-2.98)**	**1.62 (1.13-2.33)**	**1.56 (1.07-2.27)**
Ever used drug (Yes) [‡]	**2.66 (2.10-3.36)**	1.11 (0.82-1.50)	1.13 (0.84-1.53)
Ever used alcohol (Yes)	**2.94 (2.56-3.38)**	**1.91 (1.61-2.27)**	**1.98 (1.66-2.36)**
Sensation seeking (score)	**1.22 (1.19-1.25)**	**1.11 (1.08-1.15)**	**1.11 (1.08-1.14)**
susceptibility to ENDS use (score)	**1.44 (1.39-1.52)**	**1.25 (1.19-1.32)**	**1.20 (1.15-1.28)**
Overall health			
Excellent or very good	1.10 (0.92-1.31)	**1.34 (1.04-1.72)**	**1.36 (1.08-1.72)**
Good	Ref.	Ref.	Ref.
Fair or poor	1.32 (1.00-1.75)	1.16 (0.79-1.71)	1.16 (0.81-1.67)

Note: *HR=hazard ratios; [#]RHP=relative harm perception; [†]AHP=absolute harm perception; Ref.=reference group.

[†]Other tobacco products refer to cigars, smokeless tobacco, traditional cigars, filtered cigars, pipe tobacco, snus pouches, dissolvable tobacco, bids, kreteks, hookah or cigarillos.

[‡]Drug refers to marijuana, prescription drugs, cocaine or crack, stimulants, heroin, inhalants, solvents, and hallucinogens.

Bold value indicates a p-value < 0.05.

All hazard ratios and 95% confidence intervals are weighted.

Table 3. Hazard ratios (HRs) of relative harm perception on ENDS initiation among young adults (18-24 yrs).

Variables	ENDS initiation	
	Unadjusted HR* (95% CI)	**Adjusted HR (95% CI)**
Relative harm perception		
Same or more harmful	Ref.	Ref.
Less harmful	**2.30 (2.00-2.64)**	**2.01 (1.72-2.36)**
Gender (Ref.= male)		
Female	**0.82 (0.72-0.93)**	1.07 (0.92-1.23)
Race		
Non-Hispanic White	Ref.	Ref.
Non-Hispanic Black	1.08 (0.88-1.32)	1.00 (0.79-1.28)
Hispanic	**1.36 (1.19-1.56)**	1.17 (0.96-1.43)
Non-Hispanic Others	0.89 (0.65-1.20)	1.07 (0.80-1.44)
Region		
Northeast	Ref.	Ref.
Mideast	0.83 (0.69-1.00)	0.84 (0.67-1.06)
South	0.94 (0.80-1.10)	1.03 (0.85-1.25)
West	1.17 (0.90-1.51)	1.13 (0.91-1.39)
Education		
Less than high school	Ref.	Ref.
High school	1.02 (0.86-1.20)	1.24 (0.99-1.56)
Some college or college	**0.77 (0.65-0.92)**	0.92 (0.72-1.19)
Advanced degree	**0.23 (0.17-0.31)**	**0.25 (0.17-0.37)**
Poverty		
Below poverty level (< 100% of poverty guideline)	Ref.	Ref.
At or above poverty level (>= 100% of poverty guideline)	0.96 (0.84-1.10)	1.08 (0.92-1.26)
Tobacco-related attitudes		
Negative	Ref.	Ref.
Positive/Neutral	**2.35 (2.04-2.71)**	**1.53 (1.29-1.81)**
Media (Yes)	0.94 (0.75-1.18)	0.90 (0.69-1.18)
Anyone who lives with you now using tobacco (Yes)	**2.11 (1.83-2.44)**	**1.27 (1.08-1.50)**
Allowed to use tobacco inside home (Yes)	**1.53 (1.34-1.75)**	1.03 (0.88-1.21)
Health warning (Yes)	**1.35 (1.16-1.57)**	1.06 (0.90-1.25)
Ever used cigarettes (Yes)	**2.60 (2.28-2.97)**	**2.60 (1.94-3.48)**
Ever used other tobacco products (Yes) †	**1.25 (1.07-1.47)**	**2.55 (1.91-3.40)**
Ever used drug (Yes) ‡	**4.27 (3.71-4.90)**	**2.59 (2.20-3.07)**
Ever used alcohol (Yes)	**2.11 (1.68-2.65)**	**1.65 (1.29-2.11)**
Overall health		

Excellent or very good	**0.68 (0.58-0.79)**	0.89 (0.66-1.19)
Good	Ref.	Ref.
Fair or poor	1.14 (0.88-1.47)	0.80 (0.56-1.15)
Physical health		
Excellent or very good	**0.76 (0.64-0.91)**	0.97 (0.76-1.25)
Good	Ref.	Ref.
Fair or poor	1.22 (0.94-1.59)	1.02 (0.76-1.38)
Mental health		
Excellent or very good	**0.72 (0.60-0.86)**	0.97 (0.76-1.22)
Good	Ref.	Ref.
Fair or poor	1.07 (0.88-1.29)	0.86 (0.67-1.11)

Note: *HR=hazard ratios; Ref.=reference group.

†Other tobacco products refer to cigars, smokeless tobacco, traditional cigars, filtered cigars, pipe tobacco, snus pouches, dissolvable tobacco, bids, kreteks, hookah or cigarillos.

‡Drug refers to marijuana, prescription drugs, cocaine or crack, stimulants, heroin, inhalants, solvents, and hallucinogens.

Bold value indicates a p-value < 0.05.

All hazard ratios and 95% confidence intervals are weighted.

MANUSCRIPT 2

Changes in Harm Perception of ENDS and their Predictors among US Adolescents: Findings from the Population Assessment of Tobacco and Health (PATH) Study, 2013-2018

Abstract

Background: Electronic nicotine delivery systems (ENDS) use has dramatically increased in the US. This study aimed to characterize changes in ENDS harm perception over time and associated predictors among US adolescents.

Methods: Data from the 2013-2018 Population Assessment of Tobacco and Health (PATH) study for adolescents (12-17 years) were utilized. Trend analyses were employed to delineate changes in comparative and absolute ENDS harm perception over a four-year interval. We applied a time-varying effect model (TVEM) to examine the associations between the changes in harm perception and associated predictors.

Results: The results suggest that perception of ENDS as less harmful than cigarettes significantly decreased from 54.3% at Wave 1 (2013) to 30.4% at Wave 4 (2018) ($P<0.001$). Perception of ENDS as no or little harm decreased from 35.9% at Wave 1 to 16.9% at Wave 4 ($P<0.001$). These changes in harm perception were less robust among males, adolescents who did not have positive tobacco-related attitudes, and those with smoke-free home rules ($P's<0.05$). Additionally, having ever used ENDS or alcohol were more likely to be associated with reduced ENDS-related harm perception over time ($P's<0.05$).

Conclusions: Our results show that while ENDS-related harm perception have generally increased, this does not appear to be equally experienced across all adolescents, potentially highlighting the importance of at-risk groups and targets for intervention. This study can help identify individuals at risk of ENDS initiation because of their favorable ENDS harm perception profile, as well as guide the development of ENDS risk communication interventions for adolescents.

Keywords: ENDS, e-cigarettes, harm perception, public health, tobacco, adolescents

Introduction

Over the past decade, use of electronic nicotine delivery systems (ENDS; e-cigarettes) has dramatically increased in the United States (US), particularly among adolescents (Gentzke et al., 2019; Gentzke et al., 2020). As a result, ENDS are now the most commonly used nicotine products among US adolescents, with 11.3% of high school students (1.72 million) and 2.8% of middle school students (320,000) reporting current use in 2021 (Park-Lee et al., 2021). Moreover, with novel designs, the availability of appealing flavors, and minimal perception of harm, ENDS continue to attract teens, predisposing them to lifelong addiction (McKelvey et al., 2018).

While the long-term adverse effects of ENDS are unknown, accumulating evidence suggests that ENDS are not harmless (Yuan et al., 2015; USDHHS, 2016; Logue et al., 2017; NASEM, 2018; Lodrup Carlsen et al., 2018; Vogel et al., 2018; CDC, 2019; Coleman et al., 2019; O'Brien et al., 2021). ENDS contain the addictive substance nicotine and expose users to respiratory toxicants (Logue et al., 2017; Lodrup Carlsen et al., 2018; NASEM, 2018). Nicotine can affect the developing brain of adolescents (Yuan et al., 2015), and lead to lifelong nicotine dependence (Vogel et al., 2018).

Further, ENDS use is associated with an increased risk of subsequent cigarette smoking initiation (O'Brien et al., 2021), dual use (Coleman et al., 2019), and decreased smoking cessation success in real-world settings (Wallace and Foronjy, 2019).

Harm perception is an important predictor of tobacco use behavior and can influence transitions between nicotine products (Song et al., 2009; Amrock et al., 2015; Hammig et al., 2017; Persoskie et al., 2019). For example, a US nationally representative study observed that adolescents who perceived ENDS as 'little to no harm' or 'less addictive than cigarettes' were more likely to report ENDS initiation (Hammig et al., 2017). Another study among a cohort of British smokers and ex-smokers reported that perceiving ENDS as less harmful than cigarettes predicted future ENDS use in those who had never tried ENDS (Brose et al., 2015). ENDS minimal harm perception may be influenced by the active promotion of these products (Bhatnagar et al., 2014; Maziak, 2020) and may 'open the gate' for combustible cigarettes or dual use among young people (Pepper et al., 2017).

Recent trend analysis of cross-sectional data found that ENDS-related harm perception among US adolescents have increased over time (Rapp et al., 2021). As evidence regarding the deleterious health impacts of ENDS use accumulates (Yuan et al., 2015; USDHHS, 2016; Logue et al., 2017; Vogel et al., 2018; Lodrup Carlsen et al., 2018; CDC, 2019; NASEM, 2018; Coleman et al., 2019; O'Brien et al., 2021), identifying those adolescents at greatest risk of ENDS initiation based on harm perception dynamics and the associated modifiable factors linked with such perception is of importance. Initial research has identified some predictors of harm perception such as sociodemographic factors, marketing receptivity, social influences, and risk-related

behaviors (e.g., ever ENDS use and smoking status) (Pokhrel et al., 2015; Filippidis et al., 2017; Majeed et al., 2017; Yong et al., 2017; Kimber et al., 2020). However, most extant studies involved small sample sizes and/or employed cross-sectional designs (Tan et al., 2016; Czoli et al., 2017).

In this study, we used a unique cohort study of US adolescents (Population Assessment of Tobacco and Health, PATH) to characterize the changing patterns in ENDS-related harm perception at the population level and their time-varying predictors over a four-year period. Using time-varying predictors in multiple waves from PATH study allows to generate greater power for outcome variables (Baird and Maxwell, 2016). Our findings provide insights into groups at risk of ENDS use and modifiable factors that may inform intervention and prevention strategies to reduce teen ENDS use.

Methods

Study Population

We used data from the PATH Study, an ongoing, nationally representative, longitudinal cohort study of 45,971 US adolescents and adults to describe the dynamic world of tobacco use and its related health effects (Hyland et al., 2017). The PATH study uses audio computer-assisted self-interviews (ACASI) available in English and Spanish to collect self-report information on tobacco-use patterns and associated health behaviors (Hyland et al., 2017). Adolescents and adults were sampled separately. The Westat Institutional Review Board approved the study. Children ages 12 to 17 were enrolled in the study with parental permission, and all participants aged 18 and older provided informed consent. Further details of the PATH Study can be found elsewhere (Hyland et al., 2017). We examined changes in ENDS-related harm perception and associated

predictors across four data collection waves (2013-2018) among adolescent participants. The Institutional Review Board of University reviewed this study and deemed it exempt.

Study Measures

Outcomes

Comparative harm perception: This outcome was assessed prospectively across the four waves based on responses to the question, "Is using ENDS less harmful, about the same, or more harmful than smoking cigarettes?" with three categories according to literature (Amrock et al., 2015). The responses were: 1) less harmful; 2) same harmful; 3) more harmful than cigarettes.

Absolute harm perception: This outcome was assessed prospectively across the four waves based on a question, "How much do you think people harm themselves when they use ENDS." Consistent with previous studies (Parker et al., 2018; Strong et al., 2019), responses were categorized as 1) no or little harm; 2) some harm; and 3) a lot of harm.

Predictors

The selection of predictors was guided by a review of previous literature related to harm perception (Pokhrel et al., 2015; Filippidis et al., 2017; Kasza et al., 2017; Yong et al., 2017; Majeed et al., 2017; Conway et al., 2018; USDHHS, 2020; Kimber et al., 2020; Li et al., 2021) as well as the theoretical conceptual model of the PATH study (Hyland et al., 2017). Specifically, the PATH study is based on the Host, Agent, Vector, Environment (HAVE) model and how the interactions between them influence behavioral and health outcomes. Host factors are related to individuals who are tobacco users or at risk of being tobacco users including demographic characteristics. Agent factors refer to

the tobacco products' design, formulation, packaging, and promotions. Environmental factors encompass current policies, social, cultural, and geographic influences. The vector is a facilitator of interaction between host, agent, and environments.

Accordingly, *Host factors* were categorized as individual factors and risk-related behaviors in this study.

- Individual factors included sociodemographic characteristics (age, gender, race/ethnicity, region, and education), body mass index (BMI), tobacco-related attitudes and overall self-rated health (Pokhrel et al., 2015; Filippidis et al., 2017; Kasza et al., 2017; Majeed et al., 2017; Yong et al., 2017; USDHHS, 2020). For tobacco-related attitudes, participants were asked the following six questions, "1. I think I would enjoy using tobacco; 2. Using tobacco would be energizing; 3. Using tobacco would help me reduce or handle stress; 4. Using tobacco would help me calm down when I am angry; 5. Using tobacco would help me control my weight; 6. Using tobacco would help me feel more comfortable at parties". If they agreed with any of those questions, they were considered as having a positive attitude towards tobacco; otherwise, they were treated as having a negative/neutral attitude towards tobacco. For overall self-rated health, participants were asked: "In general, would you say your overall health is excellent, very good, good, fair, or poor?" and it was treated as three categories: excellent, good, and fair/poor.
- Risk-related behaviors included ENDS use, cigarette use, other tobacco product use, drug use, alcohol use, and sensation-seeking (Majeed et al., 2017; Conway et al., 2018). Participants were asked: "Have you ever used ENDS/cigarettes/other tobacco product (cigars, smokeless tobacco, traditional cigars,

filtered cigars, pipe tobacco, snus pouches, dissolvable tobacco, bids, kreteks, hookah or cigarillos)/or any substance (marijuana, prescription drugs, cocaine or crack, stimulants, heroin, inhalants, solvents, and hallucinogens)/alcohol?" For sensation-seeking, three items were assessed, and the response options for each item (1=strongly agree, 2=agree, 3=neutral, 4=disagree, 5=strongly disagree) were summed to create overall (range: 3–15) and mean scores (Conway et al., 2018). The three questions were: "1. Like to do frightening things; 2. Like new and exciting experience, even if I have to break the rules; 3. Prefer friends who are exciting and unpredictable".

Agent factors involved in this study are media use and exposure to health warnings (Li et al., 2021).

- For media use, participants were asked whether they had ever signed up for email alerts about tobacco products, read online articles about tobacco products, or watched online videos about tobacco products in the past 6 months.
- Exposure to health warnings was assessed by whether participants ever noticed health warnings on packages of ENDS and cigarettes.

Environmental factors included peer/family influence, smoke-free home rules, and parents' education (Pokhrel et al., 2015; Kimber et al., 2020; USDHHS, 2020).

- Peer/family influence was assessed using the question, "Does anyone who lives with you use any form of tobacco product?"
- Smoke-free home rules were measured among participants by whether they were allowed to use any tobacco product inside their homes.

- Parents' education was categorized as four levels: less than high school, high school, some college or college, and advanced degree.

Data analysis

The analysis plan consisted of four steps. First, we tested linear trends for the prevalence of comparative and absolute harm perception across four waves using a marginal homogeneity test. Second, for the characteristics' descriptive statistics, weighted means and standard deviations were reported for continuous variables, while frequencies and percentages were reported for categorical variables at baseline (Wave 1). Third, we combined four waves by PERSONID and excluded those participants who had missing values of outcome variables for all four waves. Finally, since we were interested in the effects of predictors on the time-variant outcomes, we used multilevel modeling as it is the most widely used analytic approach to investigate relationships between time-variant/time-invariant covariates and repeated measured outcomes (Shiyko et al., 2012).

We treated comparative and absolute harm perception as binary outcomes. Similar to previous research (Malt et al., 2020), for comparative harm perception, we combined response categories 2) and 3). 'Same or more harm than cigarettes' was used as the reference group. For absolute harm perception, we combined response categories 2) and 3). 'Some or a lot of harm' was used as the reference group. Except for gender, race, region, and parents' education, we treated other predictors (e.g., age, education, BMI, health warnings, etc.) as time-variant predictors. That is, the relationships between the predictors and the outcome could vary across the time (wave) metric and were not constrained to be equal across all four waves. In addition, due to data shortage (i.e., some questions were only asked at baseline), we used media, smoke-free home rules,

sensation-seeking, and tobacco-related attitudes only from the baseline assessment. We applied a time-varying effect model (TVEM) to our study by using the macro %TVEM (available from http://methodology.psu.edu) and the p-spline estimation method (Shiyko et al., 2012). The macro %TVEM uses all available data for every individual over time; however, time-specific observations with missing values (predictor or outcome) are automatically excluded (Dermody and Shiffman, 2020). Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are reported. The level of statistical significance used was α=0.05 for 2-sided tests for all analyses. Data analyses were conducted using SAS version 9.4 statistical software and Epi Info 7.2.4.0 (CDC, Atlanta, GA).

Results

Baseline characteristics

Among 11,226 adolescents included in this study at Wave 1, 54.3% reported perceiving ENDS as less harmful than cigarettes and 35.9% reported perceiving ENDS as having no or little harm. More than half of the adolescents were male (51.5%), Non-Hispanic White (56.5%), aged 15–17 years (52.3%) and in 9–12 grade education level (65.1%). Additionally, most of the study participants were not allowed to use tobacco inside their homes (71.0%), did not have positive tobacco-related attitudes (76.1%), had never used ENDS (87.2%), alcohol (58.3%) or cigarettes (84.5%). More detailed information about this sample is presented in **Table 1**.

Trends of changes in harm perception

Comparative harm perception

The proportion of individuals who perceived ENDS as less harmful than cigarettes significantly decreased from 54.3% (95%CI, 53.8%-54.9%) at Wave 1 to 30.4% (95%CI, 29.5%-31.2%) at Wave 4 (P<0.001). The proportion of individuals who perceived ENDS as having the same degree of harm as cigarettes significantly increased from 40.9% (95%CI, 40.4%-41.4%) to 58.4% (95%CI, 57.5%-59.2%) over the same period (P=0.003) (**Figure 1A**).

Absolute harm perception

A positive change in absolute harm perception was also noticed. Specifically, the proportion of individuals who perceived ENDS as having no or little harm decreased from 35.9% (95%CI, 35.4%-36.4%) at Wave 1 to 16.9% (95%CI, 16.3%-17.6%) at Wave 4 (P<0.001). Individuals who perceived ENDS as having a lot of harm increased from 22.6% (95%CI, 22.0%-23.2%) at Wave 1 to 50.9% (95%CI, 50.0%-51.8%) at Wave 4 (P<0.001) (**Figure 1B**).

Predictors of changes in harm perception

Comparative harm perception

Table 2 shows the results for the baseline predictors of the ENDS comparative harm perception. Specifically, participants who were males (OR = 1.66; 95%CI: 1.60–1.73), who did not hold positive tobacco-related attitudes (OR = 1.45; 95%CI: 1.37–1.53), who had smoke-free home rules (OR = 1.14; 95%CI: 1.08–1.19), and whose parents' education was higher than high school, were more likely to perceive lower comparative harm over time. Hispanics (vs. Non-Hispanic Whites) (OR = 0.81; 95%CI: 0.77–0.85) and those who had higher sensation-seeking scores (OR = 0.94; 95%CI: 0.93–0.95) were less likely to report lower comparative harm perception over time.

No significant association was noticed between region and comparative harm perception (P's > 0.05).

Table 3 and **Supplemental Figure 1** show the time-variant predictors of the ENDS comparative harm perception. Ever ENDS use was associated with a higher likelihood in perceiving lower comparative harm from Wave 1 (OR = 2.61; 95%CI: 1.75–3.90) to Wave 4 (OR = 2.90; 95%CI: 2.13–3.95). Ever alcohol use was associated with a higher likelihood in perceiving lower comparative harm from Wave 2 (OR = 1.61; 95%CI: 1.34–1.94) to Wave 4 (OR = 2.90; 95%CI: 2.13–3.95). Ever cigarettes use was associated with a lower likelihood in perceiving lower comparative harm from Wave 2 (OR = 0.67; 95%CI: 0.48–0.93) to Wave 4 (OR = 0.44; 95%CI: 0.31–0.61).

Absolute harm perception

Besides the similar predictors observed for comparative harm perception (e.g., males, holding none-positive tobacco-related attitudes and having smoke-free home rules), Non-Hispanic Blacks (vs. Non-Hispanic Whites) (OR = 1.42; 95%CI: 1.33–1.52) were more likely to perceive lower absolute harm over time (**Table 2**). No significant association was found between region and absolute harm perception (P's > 0.05). Ever ENDS use was associated with a higher likelihood in perceiving lower absolute harm from Wave 1 (OR = 4.61; 95%CI: 3.14–6.76) to Wave 4 (OR = 3.16; 95%CI: 2.20–4.55). Living with anyone who used tobacco was associated with a higher likelihood in perceiving lower absolute harm from Wave 1 (OR = 1.66; 95%CI: 1.41–1.95) to Wave 3 (OR = 1.28; 95%CI: 1.04–1.57). Ever alcohol use was associated with a higher likelihood in perceiving lower absolute harm from Wave 3 (OR = 1.39; 95%CI: 1.11–1.73) to Wave

4 (OR = 1.41; 95%CI: 1.13–1.74). For other time-variant predictors of comparative and absolute harm perception, please see **Table 3** and **Supplemental Figure 2**.

Discussion

As harm perception represents an important determinant of tobacco products initiation, this study's main goals were to characterize changes in ENDS-related harm perception between 2013 and 2018, and its predictors. Generally, adolescents in our cohort showed increased ENDS-related harm perception, either in comparative or absolute terms. In 2013, about 54.3% of adolescents perceived ENDS as less harmful than cigarettes and this number declined to 30.4% in 2018. Perceiving ENDS as having no or little harm also decreased during the same period. These changes in harm perception were less robust among males, those who did not have positive tobacco-related attitudes, and those who had smoke-free home rules. In addition, some predictors seem to influence the lack of changes in harm perception such as living with someone who used tobacco or having ever used ENDS or alcohol. These findings provide information regarding the evolution of ENDS harm perception in the real-world setting and may help identify individuals at risk of ENDS initiation because of their favorable ENDS harm perception profile, as well as guide the development of ENDS risk communication interventions for adolescents.

We observed that males were more likely than females to perceive ENDS as a reduced harm product, which is consistent with the previous literature (Amrock et al., 2015; Rapp et al., 2021). This can stem from industry advertisements since research suggests that ENDS are more targeted to males than females (Richardson et al., 2015). Moreover, compared to females, males tend to voluntarily engage in risky behaviors

more frequently, which could be due to the shared peer norms (Croisant et al., 2013). Minority adolescents such as Non-Hispanic Blacks were less likely to perceive health risks of nicotine or toxicants in ENDS compared to their White peers (Vu et al., 2020); this may help explain why they were more likely to report ENDS as having no or little harm over time. Aligning with existing literature (Majeed et al., 2017), our study found no association between region and harm perception. However, those whose parents had a higher education level were more likely to perceive lower ENDS comparative harm. This is probably due to the available knowledge about the harms of different tobacco products (USDHHS, 2016; NASEM, 2018). Traditional education and harm perception of tobacco products are closely associated. When it comes to ENDS perception, it is likely that those educated parents had more access to perceive harm reduction knowledge on ENDS use compared to cigarettes.

Interestingly, our study showed that holding none-positive tobacco-related attitudes and smoke-free home rules were associated with reduced ENDS harm perception, contrary to what one would expect. However, it is important to differentiate between the regulatory classification of ENDS as a tobacco product and their public perception. Evidence shows that many ENDS users do not consider ENDS as a tobacco product, but a healthier alternative to traditional cigarettes (Notley et al, 2018; Munafò, 2019). In this context, heightened concern about combustible tobacco products can translate into more appreciation of ENDS and a lenient attitude towards them. Furthermore, adolescents with higher sensation-seeking scores were correlated with higher ENDS comparative harm perception over time, which aligns with a previous study (Case et al., 2017), indicating adolescents may still want to take risks for the sake of

using ENDS despite knowledge of potential harmful effects. Adolescence is a critical period for initiating risk behaviors such as smoking, and these unhealthy behaviors may continue into adulthood (Tucker et al., 2005). These findings point towards those adolescents potentially at a higher risk of ENDS use and may motivate future studies among these specific groups.

We also noticed that adolescents who had ever used ENDS or alcohol were consistently associated with perceiving lower absolute harm across time. This needs to be addressed by policymakers since perceiving ENDS as reduced harms among alcohol users may predispose adolescents to ENDS initiation and dual or multiple substance use (Parikh and Bhattacharyya, 2018; Wong and Fan, 2018). Additionally, although the odds decreased over time, adolescents who lived with a tobacco user were correlated with lower absolute harm perception, which indirectly reflects the importance of parental/peer influence on adolescent risk behaviors. Future cohort studies are particularly needed in further investigating and monitoring these factors to understand the mechanisms of how these modifiable factors influence harm perception changes over time.

Accumulating evidence indicates that ENDS reduced harm perception is associated with future ENDS use among adolescents (Brose et al., 2015; Perikleous et al., 2018). Currently, time trends of ENDS harm perception lie in contrast with their increasing initiation among young people (Rapp et al., 2021). This may be attributable to other factors that are attracting young people to these products in the face of increased awareness of their harmful potential (Rapp et al., 2021). In particular, flavor, appealing design, and intensive marketing on social media are likely driving the use of ENDS among adolescents (Jenssen and Boykan, 2019). Such understanding of the drivers of

ENDS use points towards the need for comprehensive efforts to reduce the spread of ENDS. As the US Food and Drug Administration (FDA) has started such work by raising the age for ENDS purchase to 21 and restricting flavors, devoting more efforts to counter-marketing and risk communication strategies (FDA, 2018; FDA, 2019; FDA, 2020). Currently, the FDA requires that ENDS packages display textual health warning about the addictiveness of nicotine (FDA, 2018). However, this is inadequate considering the multi-faceted harm profile of ENDS (NASEM, 2018; USDHHS, 2016), and the known that higher effectiveness of graphic health warning labels. A pilot study conducted by our team showed that exposure to graphic health warnings on ENDS products could impact users' harm perception of ENDS among young people more than the FDA text-only messages (Li et al., 2021). Future studies are continuously needed to examine the efficacious interventions regarding ENDS-specific health warnings in reducing ENDS use at both individual and population levels.

This study has some limitations. First, the harm perception of ENDS use was assessed using a generic question, which may not capture various specific aspects of harms associated with ENDS use. Second, not all the variables used were assessed in a time-varying way. For example, we only used Wave 1 data for the media variable since it was only asked at baseline. Further, limited by the PATH study design, some of the variables were not asked for ENDS-specific questions. For example, the media variable was asked in tobacco-related questions rather than ENDS-specific questions as well as measured not only in one direction (i.e., perceived either positive or negative news). Future studies need to consider these limitations of study design and incorporate the specific questions regarding ENDS use when assessing the relationship between factors

and harm perception changes. Fourth, the rapid product innovation and development in the ENDS marketplace made it difficult to identify the consistent terminology regarding ENDS. For example, in Wave 2, the questions about ENDS were replaced by a more generic question about the use of any ENDS (i.e., ENDS, e-cigars, e-hookahs, etc.) to capture newer generations of vaping products. However, the expansion of the definition for ENDS will unlikely affect our analysis as it encompasses the most popular forms of ENDS. On the other hand, using the nationally representative longitudinal data (PATH) with a focus on tobacco use and associated factors, allows us to monitor important trends of ENDS harm perception and the factors related to ENDS use in a real-world setting.

Conclusions

Our study showed that US adolescents have become more aware of ENDS harms over time. These changes in harm perception were less noticeable among those who were males, did not have positive tobacco-related attitudes, had smoke-free home rules, ever used ENDS or alcohol, and lived with someone who used tobacco. Such results not only highlight some of the common patterns shared with other tobacco products but also underscore the unique factors specific to ENDS. The promotion of ENDS as a reduced harm product or healthier alternative to traditional tobacco can underlie the discrepancy we found between none-positive attitudes towards tobacco products and appreciation of ENDS as reduced harm products. While further studies can help clarify the drivers of attitudes towards different tobacco products, our results offer a nuanced picture that can inform unique interventions to reduce ENDS, as well as groups that are well situated to benefit from such interventions.

It also has implications for future monitoring of tobacco products harm perception by studies like the PATH, which should differentiate between the assessment of ENDS-related questions (e.g., attitudes) from those of combustible tobacco products.

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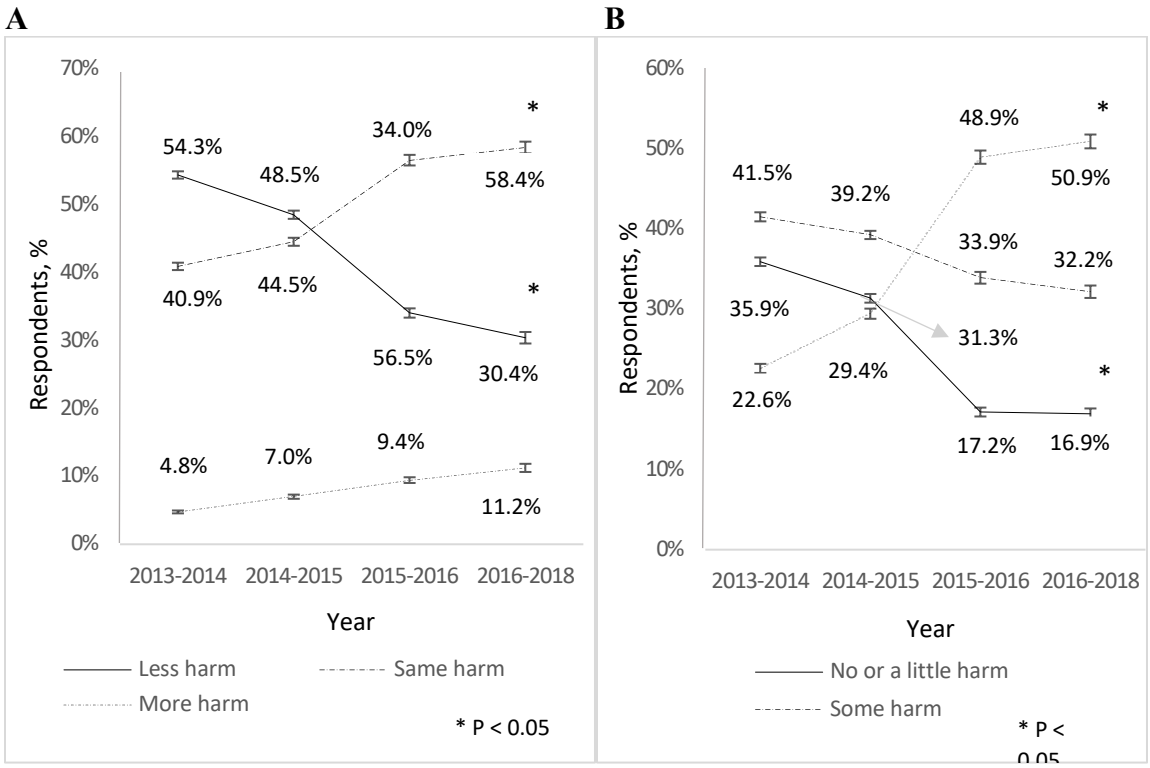
Figures and Tables

Figure 1. Comparative harm perception of ENDS in adolescents (12-17yrs) (panel A); Absolute harm perception of ENDS in adolescents (12-17yrs) (panel B): Population Assessment of Tobacco and Health study, 2013-2018.



Percentages are weighted. Error bars indicate 95% CIs.

Table 1. Baseline descriptive statistics for US adolescents (12-17 years): Population Assessment of Tobacco and Health study, 2013-2014.

Participant Characteristics	Unweighted [a] n	Weighted [b] % (95% CI)
Total	11226	100.0
Comparative harm perception		
Less harmful	6038	54.3 (53.3-55.4)
Same harmful	4621	40.9 (39.8-42.0)
More harmful	567	4.8 (4.3-5.2)
Absolute harm perception		
No or little harm	4013	35.9 (34.8-37.0)
Some harm	4615	41.5 (40.4-42.7)
A lot of harm	2500	22.6 (21.4-23.7)
Age		
12-14	5439	47.7 (47.3-48.2)
15-17	5787	52.3 (51.8-52.7)
Gender (Male)	5749	51.5 (51.1-51.8)
Race		
Non-Hispanic White	5652	56.5 (56.0-56.9)
Non-Hispanic Black	1484	13.5 (13.1-13.8)
Hispanic	3073	21.3 (20.8-21.7)
Non-Hispanic Others	1017	8.8 (8.5-9.1)
Region		
Northeast	1736	17.2 (16.7-17.6)
Mideast	2473	21.9 (21.5-22.3)
South	4204	37.4 (35.9-37.9)
West	2813	23.5 (23.0-24.1)
Education		
6-8 grade	3965	34.9 (34.3-35.6)
9-12 grade	7233	65.1 (64.4-65.7)
BMI kg/m^2 (<30.0)	9997	91.2 (90.5-91.9)
Tobacco-related attitudes		
Positive/Neutral	2668	23.9 (23.0-24.9)
Negative	8551	76.1 (75.1-77.0)
Media (Yes)	544	5.2 (4.8-5.6)
Anyone who lives with you now using tobacco (Yes)	4243	37.0 (35.1-38.9)
Allowed to use tobacco inside home (Yes)	3261	29.0 (27.6-30.4)
Health warning (Yes)	5842	52.7 (51.3-54.0)
Parents' education		
Less than high school	2220	17.3 (16.0-18.5)
High school	2134	18.4 (17.2-19.5)
Some college or college	5718	53.3 (51.7-54.9)

Advanced degree	1073	11.1 (9.8-12.4)
Ever used ENDS (Yes)	1429	12.8 (12.0-13.5)
Ever used cigarettes (Yes)	1752	15.5 (14.6-16.5)
Ever used other tobacco products (Yes)	492	4.4 (3.9-4.9)
Ever used drug (Yes)	749	7.3 (6.6-8.0)
Ever used alcohol (Yes)	4574	41.7 (40.1-43.2)
Sensation seeking (score)*	11076	9.91 ± 0.03
Overall health		
Excellent or very good	9591	87.1 (86.3-87.9)
Good	1271	10.4 (9.7-11.1)
Fair or poor	319	2.4 (2.1-2.7)

[a]Represents unweighted sample in numbers (numbers may not sum to the total due to missing data).
[b]Represents weighted sample in percentage (%) and 95% confident interval (95%CI) or mean and standard deviation (SD) for the US adolescent population from PATH.
[*]Data presented as mean (SD).

Table 2. Time-invariant and time-variant predictors of ENDS harm perception among US adolescents: longitudinal analysis of the Population Assessment of Tobacco and Health study, 2013-2018.

Predictor variables	Comparative harm perception[#] AOR (95%CI)	Absolute harm perception[#] AOR (95%CI)
Time-invariant predictors		
Gender (Male vs Female)	**1.66 (1.60-1.73)****	**1.65 (1.57-1.72)****
Race		
Non-Hispanic White	Ref.	Ref.
Non-Hispanic Black	0.99 (0.93-1.05)	**1.42 (1.33-1.52)****
Hispanic	**0.81 (0.77-0.85)****	1.08 (1.02-1.14)
Non-Hispanic Others	0.98 (0.92-1.05)	1.12 (1.04-1.21)
Region		
Northeast	Ref.	Ref.
Mideast	1.12 (1.05-1.20)	1.11 (1.04-1.20)
South	1.04 (0.98-1.10)	1.07 (1.00-1.14)
West	0.88 (0.83-0.94)	0.94 (0.88-1.01)
Parents' education		
Less than high school	Ref.	Ref.
High school	1.11 (1.04-1.18)	1.09 (1.02-1.18)
Some college or college	**1.22 (1.15-1.30)****	1.08 (1.01-1.14)
Advanced degree	**1.21 (1.12-1.30)***	0.88 (0.80-0.96)
Time-variant predictors (baseline only)[†]		
Tobacco-related attitudes (Negative vs Positive)	**1.45 (1.37-1.53)****	**1.41 (1.33-1.49)****
Media (Yes vs No)	0.97 (0.89-1.05)	0.95 (0.86-1.04)
Allowed using tobacco inside home (Yes vs No)	**1.14 (1.08-1.19)****	**1.31 (1.24-1.38)****
Sensation seeking (score)	**0.94 (0.93-0.95)****	**0.94 (0.93-0.95)****

[†]Time-variant predictors that were assessed from baseline only since the data were not available in the subsequent waves.

[#]The reference group for comparative harm perception is ENDS as same or more harmful than cigarettes and for absolute harm perception is ENDS as some or a lot of harm.

AOR= Adjusted Odds Ratio; CI= Confidence Interval; Ref.= Reference category

NOTE: Bold estimates indicate statistical significance at P<0.05. *P<0.05, **P<0.001

Table 3. Time-variant predictors† of ENDS harm perception among US adolescents: longitudinal analysis of the Population Assessment of Tobacco and Health study, 2013-2018.

Predictor variables	Time (2013-2018) Wave 1 AOR (95%CI)	Wave 2 AOR (95%CI)	Wave 3 AOR (95%CI)	Wave 4 AOR (95%CI)
Comparative harm perception#				
Age (15-17 vs 12-14)	0.99 (0.69-1.43)	0.93 (0.78-1.12)	0.97 (0.81-1.17)	0.84 (0.53-1.31)
Education (9-12 vs 6-8 grade)	1.06 (0.90-1.25)	1.15 (0.96-1.37)	1.32 (1.00-1.73)	1.11 (0.53-2.33)
BMI kg/m^2 (>= 30.0 vs < 30.0)	1.10 (0.84-1.45)	0.78 (0.60-1.03)	0.80 (0.61-1.06)	**0.72 (0.53-0.97)***
Anyone who lives with you now using tobacco (Yes vs No)	**1.32 (1.13-1.54)***	**1.30 (1.11-1.54)***	1.09 (0.92-1.28)	1.12 (0.94-1.35)
Health warning (Yes vs No)	0.95 (0.83-1.10)	1.02 (0.88-1.18)	0.91 (0.78-1.06)	0.95 (0.80-1.11)
Ever used ENDS (Yes vs No)	**2.61 (1.75-3.90)***	**2.33 (1.79-3.04)***	**2.84 (1.55-5.21)***	**2.90 (2.13-3.95)***
Ever used cigarettes (Yes vs No)	0.78 (0.54-1.12)	**0.67 (0.48-0.93)***	**0.55 (0.30-0.99)***	**0.44 (0.32-0.61)***
Ever used other tobacco products (Yes vs No)	1.63 (0.89-2.97)	1.20 (0.70-2.07)	0.70 (0.41-1.20)	0.98 (0.60-1.60)
Ever used drug (Yes vs No)	0.99 (0.60-1.64)	1.34 (0.87-2.08)	1.11 (0.80-1.54)	1.18 (0.90-1.54)
Ever used alcohol (Yes vs No)	1.13 (0.96-1.33)	**1.61 (1.34-1.94)***	**1.89 (1.60-2.25)***	**1.93 (1.62-2.29)***
Overall health				
Excellent or very good	0.96 (0.76-1.20)	0.96 (0.80-1.15)	0.97 (0.81-1.17)	**0.68 (0.55-0.82)***
Good	Ref.	Ref.	Ref.	Ref.
Fair or poor	1.09 (0.65-1.83)	0.79 (0.56-1.12)	0.91 (0.63-1.31)	0.92 (0.62-1.35)
Absolute harm perception#				
Age (15-17 vs 12-14)	1.34 (0.91-1.96)	1.08 (0.89-1.32)	0.97 (0.77-1.24)	1.31 (0.75-2.30)

Education (9-12 vs 6-8 grade)	1.00 (0.84-1.18)	1.03 (0.85-1.26)	0.88 (0.63-1.22)	0.83 (0.35-2.00)
BMI kg/m^2 (>= 30.0 vs < 30.0)	1.02 (0.77-1.35)	0.84 (0.63-1.13)	0.90 (0.64-1.26)	0.90 (0.63-1.28)
Anyone who lives with you now using tobacco (Yes vs No)	**1.66 (1.41-1.95)***	**1.37 (1.15-1.64)***	**1.28 (1.04-1.57)***	1.14 (0.92-1.41)
Health warning (Yes vs No)	1.04 (0.90-1.21)	1.10 (0.93-1.29)	1.10 (0.91-1.34)	1.07 (0.88-1.31)
Ever used ENDS (Yes vs No)	**4.61 (3.14-6.76)***	**3.04 (2.37-3.90)***	**4.69 (2.08-10.61)***	**3.16 (2.20-4.55)***
Ever used cigarettes (Yes vs No)	1.03 (0.70-1.50)	1.26 (0.92-1.73)	0.58 (0.26-1.30)	0.73 (0.50-1.06)
Ever used other tobacco products (Yes vs No)	**2.09 (1.19-3.65)***	**2.00 (1.20-3.32)***	1.07 (0.55-2.07)	1.01 (0.56-1.83)
Ever used drug (Yes vs No)	1.27 (0.75-2.14)	**1.63 (1.08-2.46)***	1.00 (0.68-1.46)	1.07 (0.79-1.46)
Ever used alcohol (Yes vs No)	1.08 (0.90-1.28)	1.19 (0.98-1.45)	**1.39 (1.11-1.73)***	**1.41 (1.13-1.74)***
Overall health				
Excellent or very good	**0.67 (0.54-0.85)***	0.93 (0.76-1.13)	**0.76 (0.61-0.96)***	0.91 (0.71-1.17)
Good	Ref.	Ref.	Ref.	Ref.
Fair or poor	**0.57 (0.33-0.99)***	1.09 (0.76-1.57)	1.27 (0.85-1.91)	0.94 (0.57-1.54)

[†]Time-variant predictors were assessed from all four waves.

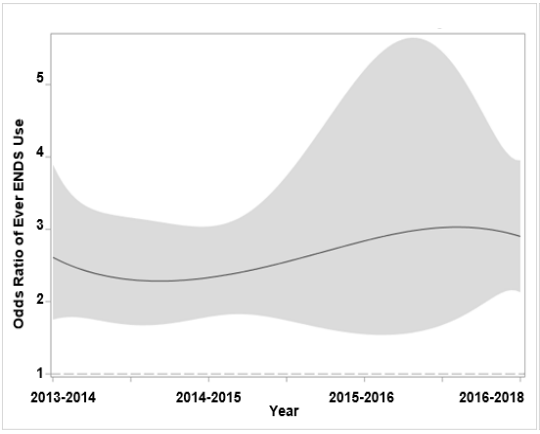
[#]The reference group for comparative harm perception is ENDS as same or more harmful than cigarettes and for absolute harm perception is ENDS as some or a lot of harm.

AOR= Adjusted Odds Ratio; CI= Confidence Interval; Ref.= Reference category

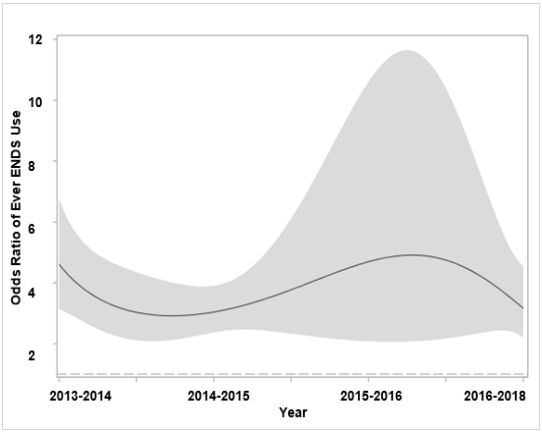
NOTE: Bold estimates indicate statistical significance at *P<0.05.

Supplemental Figure 1. Significant time-variant predictors† of ENDS harm perception among US adolescents: longitudinal analysis of the Population Assessment of Tobacco and Health study, 2013-2018.

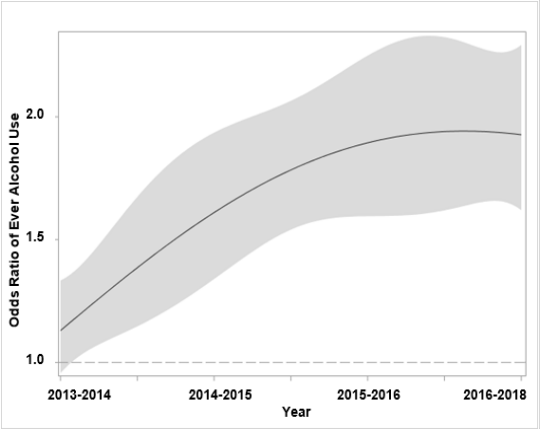
A1: Ever ENDS Use



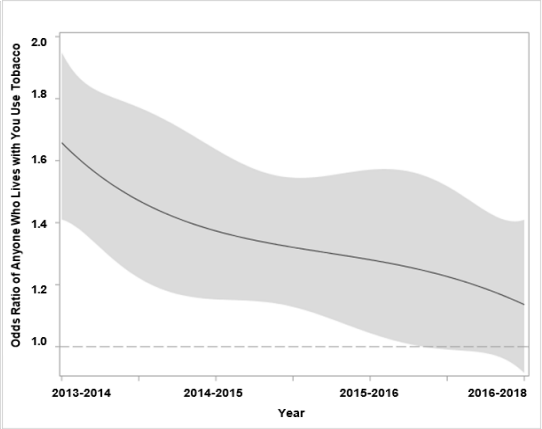
B1: Ever ENDS Use



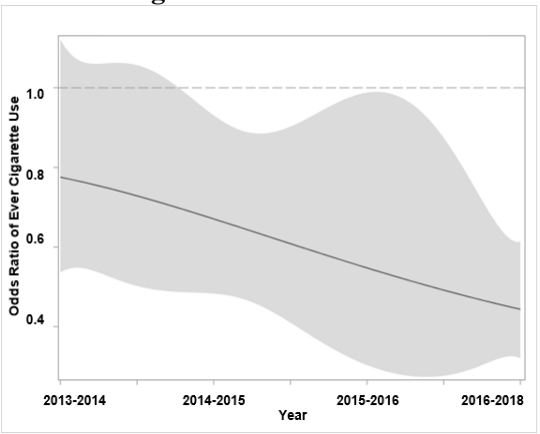
A2: Ever Alcohol Use



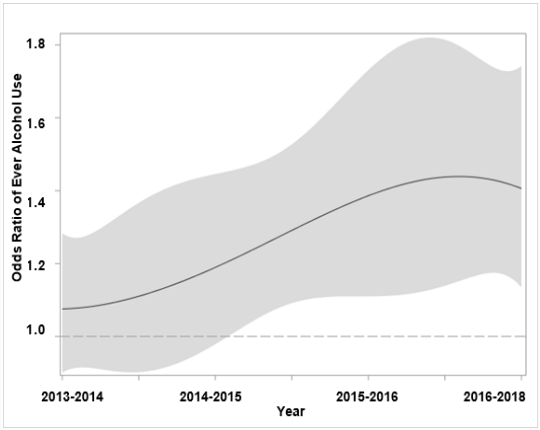
B2: Anyone Who Lives with You Use Tobacco



A3: Ever Cigarette Use



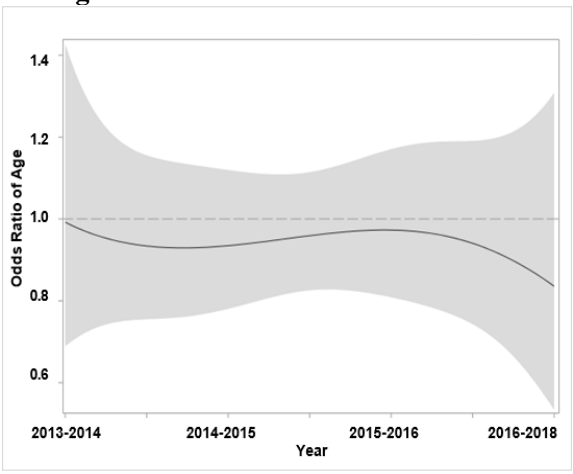
B3: Ever Alcohol Use



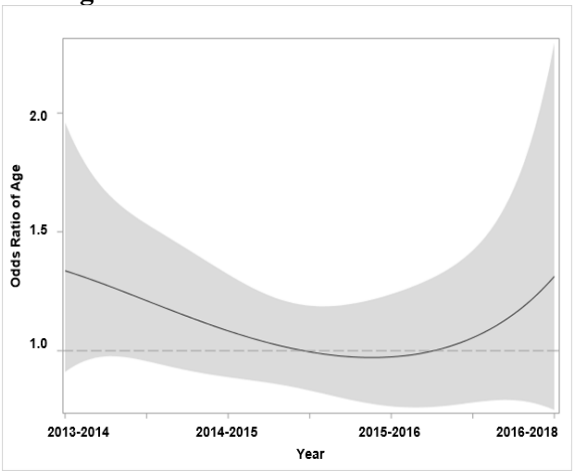
†Time-variant predictors were assessed from all four waves. NOTE: These are graphical summaries of intercept functions (odds ratios with confidence intervals), representing a time-varying level of predictors of harm perceptions of ENDS. A1-A3 represent significant time-variant predictors for comparative harm perception; B1-B3 represent significant time-variant predictors for absolute harm perception. The central solid line indicates the point estimate of the odds ratio, and the gray ribbon with dashed borders shows the 95% confidence interval. The horizontal dotted line shows the odds ratio of 1 (no predictive validity).

Supplemental Figure 2. Non-significant time-varying predictors† of harm perception of ENDS among US adolescents: longitudinal analysis of the Population Assessment of Tobacco and Health study, 2013-2018.

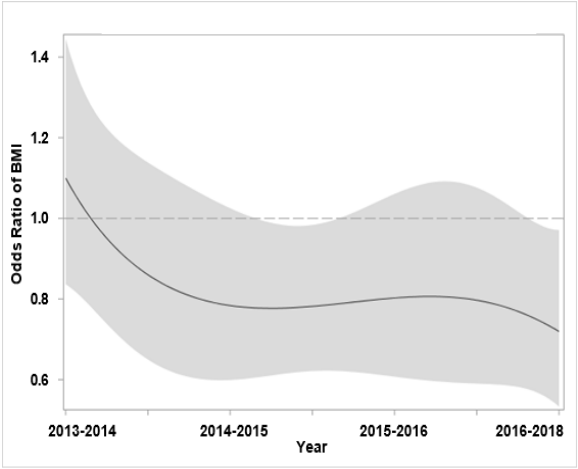
A1: Age



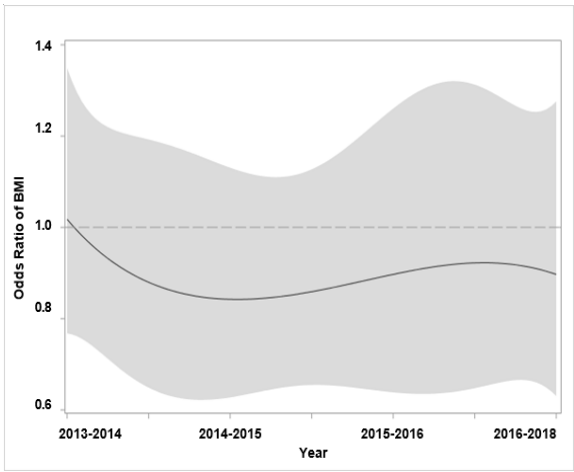
B1: Age



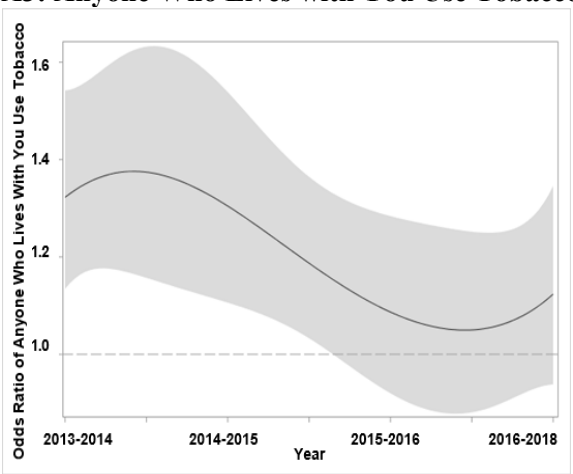
A2: BMI



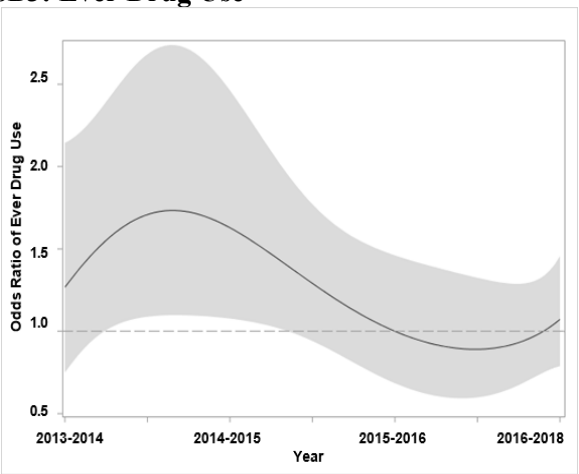
B2: BMI



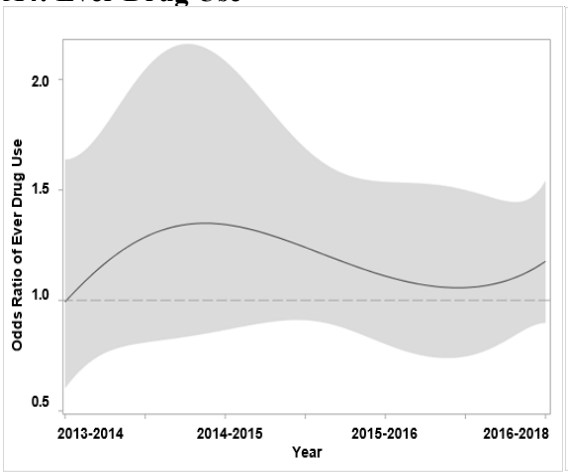
A3: Anyone Who Lives with You Use Tobacco



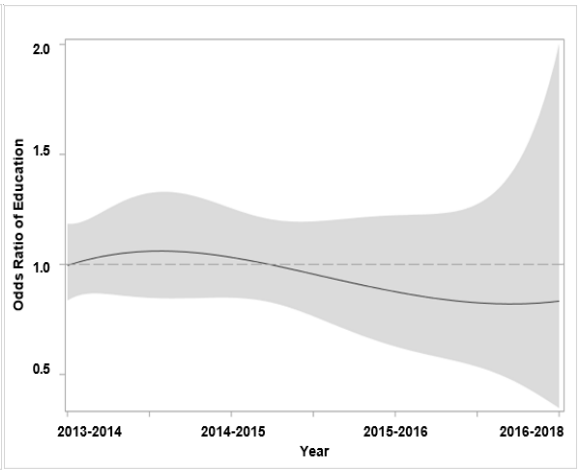
B3: Ever Drug Use



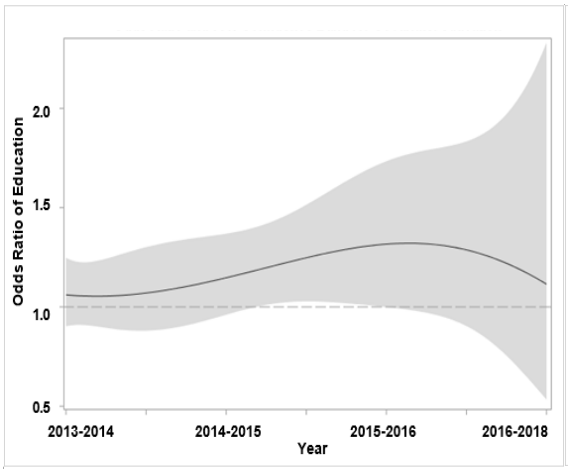
A4: Ever Drug Use



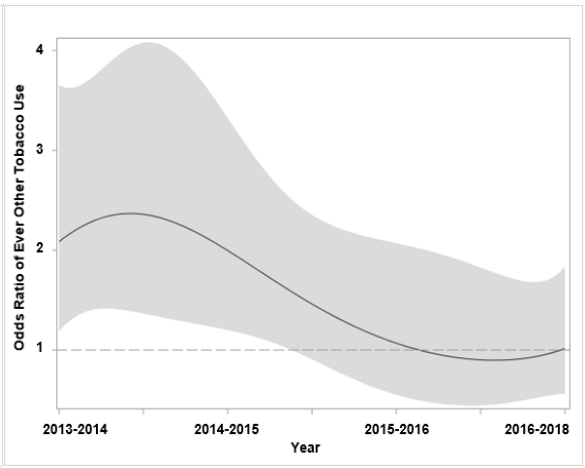
B4: Education



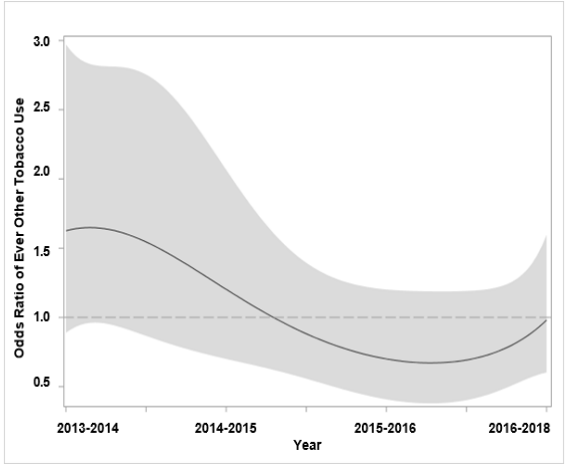
A5: Education



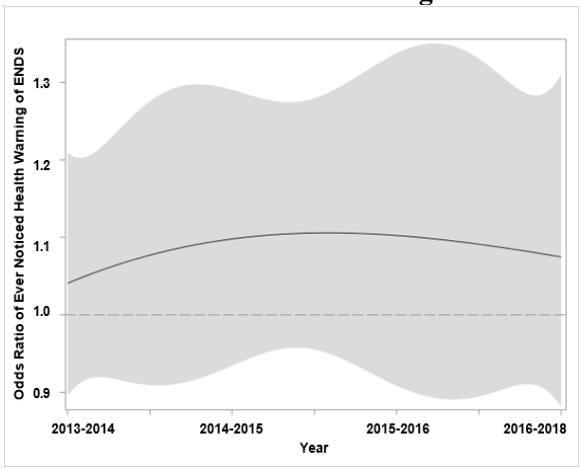
B5: Ever Other Tobacco Use



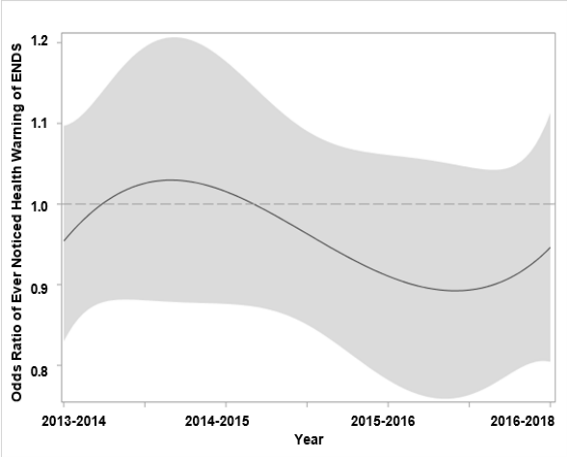
A6: Ever Other Tobacco Use



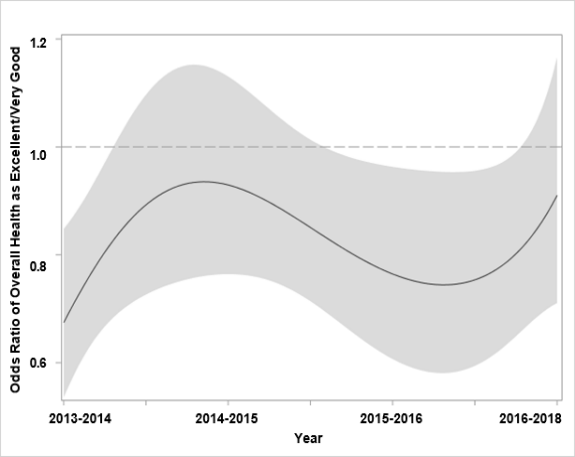
B6: Ever Noticed Health Warning of ENDS



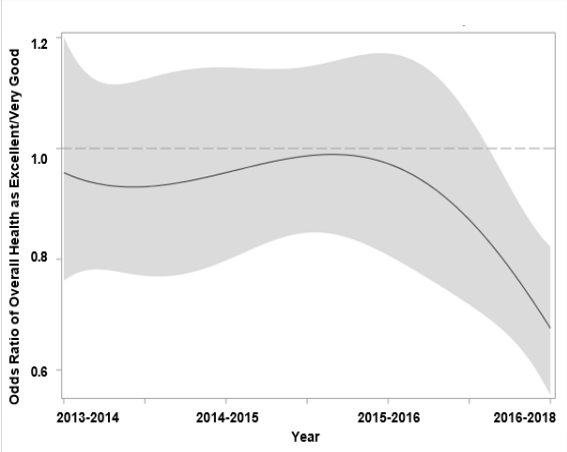
A7: Ever Noticed Health Warning of ENDS



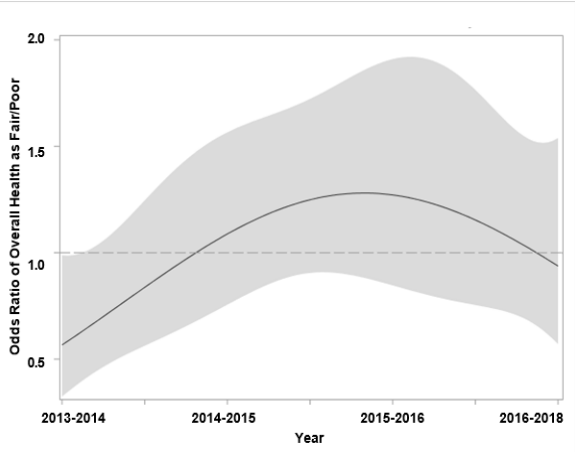
B7: Overall Health as Excellent/Very Good



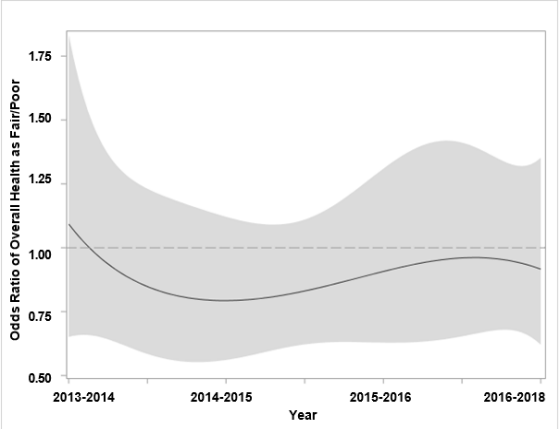
A8: Overall Health as Excellent/Very Good



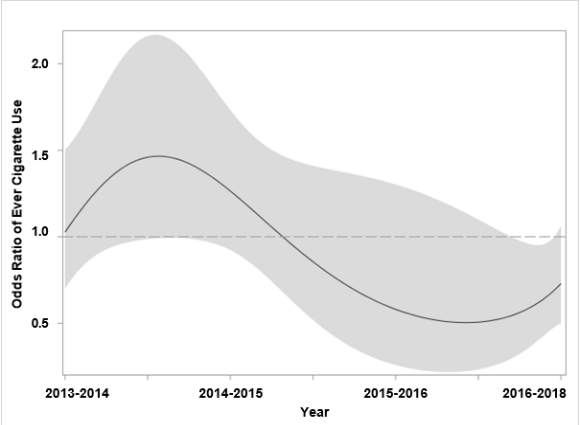
B8: Overall Health as Fair/Poor



A9: Overall Health as Fair/Poor



B9: Ever Cigarette Use



†Time-variant predictors were assessed from all four waves.

NOTE: These are graphical summaries of intercept functions (odds ratios with confidence intervals), representing a time-varying level of predictors of harm perceptions of ENDS. A1-A9 represent non-significant time-variant predictors for comparative harm perception; B1-B9 represent non-significant time-variant predictors for absolute harm perception. The central solid line indicates the point estimate of the odds ratio, and the gray ribbon with dashed borders shows the 95% confidence interval. The horizontal dotted line shows the odds ratio of 1 (no predictive validity).

MANUSCRIPT 3

The Effect of Graphic Health Warning Labels Placed on the ENDS Device on Young Adult Users' Experience, Exposure and Intention to Use: A Pilot Study

Abstract

Objective: This proof-of-concept study aims to evaluate the effect of placing graphic health warning labels (GHWLs) on the ENDS device on users' experience, puffing patterns, harm perception, nicotine exposure, and intention to quit or use in the future.

Methods: JUUL users (n=26, age 18-24 years; 69% male; 85% Hispanic) were recruited to complete two 60 minutes *ad libitum* sessions that differed by GHWL on the device (GHWL vs. no-GHWL control) in an experimental clinical lab study.

Results: Compared to the control session, using JUUL with GHWL on the device was significantly associated with reduced positive experience such as pleasure, product liking, and user satisfaction (p-value< 0.05 for all). Also, after exposure to GHWL, participants were less interested in using the same product again (p-value= 0.007), even if it was the only product available on the market compared to control (p-value= 0.03). Trends towards reduced puffing behavior and nicotine boost were also noted during the GHWL, compared to control sessions.

Conclusions: This pilot study shows that placing GHWL on the ENDS device may be an effective and promising strategy to reduce ENDS use among young people.

Keywords: E-cigarettes; ENDS; JUUL device; Graphic health warning labels; Young adults

Introduction

The use of electronic nicotine delivery systems (ENDS; e-cigarettes) has reached epidemic levels among young people (US Department of Health and Human Services, 2016). ENDS are now the leading tobacco/nicotine product among young people in the United States (US), where 19.6% of high school students in 2020 (Wang et al., 2020) and 7.6% of young adults (18-24 years) in 2018 were current ENDS users (Dai & Leventhal, 2019a). Young people are particularly prone to ENDS use due to their novelty, social acceptability, flavors, misperception of safety, and targeted industry marketing (Soule et al., 2016). Accumulating evidence shows that ENDS emit toxic substances, and their use is associated with nicotine dependence, respiratory symptoms, and increased risk of cigarette smoking initiation among young people (US Department of Health and Human Services, 2016). Accordingly, there is an urgent need to respond to the ENDS use epidemic among US youth (Center for Diseases Control and Prevention, 2020).

The marketing of ENDS as safe or safer alternatives to cigarettes is a potentially important driver of ENDS popularity among youth (e.g., Klein et al., 2016). For example, a survey of 445 young people in California found that the perceived chance of experiencing short and long-term risks from ENDS was 40% (McKelvey et al., 2018). Additionally, a systematic review reported lower perceived harm and addictiveness of ENDS compared to cigarettes among those exposed to ENDS marketing (Collins et al., 2019). Therefore, communicating risks associated with ENDS use has been identified as a top priority to reduce ENDS use among young people in the US (Center for Diseases Control and Prevention, 2020).

Graphic health warning labels (GHWLs) represent one of the most promising tobacco control strategies to communicate smoking-related risks. Studies have consistently demonstrated that GHWLs are associated with a decrease in smoking rates, smoking-related morbidity and mortality (Huang et al., 2014; Green et al., 2016; Noar et al., 2016a) as well as diminished smoking subjective experience in cigarettes use (e.g., willingness and intention to smoke) (Schneider et al., 2012; Blanton et al., 2014; Evans et al., 2015). This line of research can be guided by the message impact framework, which assumes that features of the health warnings will lead to behavioral changes through five main psychological events including; attention; reaction; harm perception; intention to change; and behavior change (e.g., reducing use or quitting) (Noar et al., 2016b). Specifically, through these psychological steps that involve increased attention about behavior-related hazards, as well as eliciting fear and other negative affect in association with behavior, GHWLs are believed to drive behavioral change (e.g., reduced use willingness) and quitting in populations (Hammond et al., 2003; Hammond, 2011; Noar et al., 2016a; Noar et al., 2016b).

Experts in cigarette warning label research suggest that GHWLs could also be considered for ENDS (Sontag et al., 2019). However, the legitimate concerns have been voiced that health warnings for ENDS can lead to behavioral changes like more cigarette smoking or discouraging adult smokers from using them to wean off smoking due to the reduced appeal of ENDS (Pacek et al., 2019). Complicating matters, these concerns need to be weighed against the massive uptake of ENDS use among young people and the highly addictive levels of nicotine in some of the most popular disposable ENDS products such as JUUL (Reilly et al., 2019; Herzog & Nielsen, 2019).

In fact, a significant proportion (63%) of these young ENDS users are unaware these products contain nicotine (Willett et al., 2019).

Starting in 2018, the US Food and Drug Administration (FDA) required that ENDS packages display a black and white textual health warning label "*WARNING: This product contains nicotine. Nicotine is an addictive chemical*". While this represents a good first step, evidence shows the superior performance of GHWLs over text (Noar et al., 2016a; Sontag et al., 2019), and that warning of harms beyond nicotine is more effective (Brewer et al., 2019; Sontag et al., 2019; Wackowski et al., 2019). For example, a recent study reported that GHWLs are more effective than the text-only warning version in a series of ENDS use outcomes (e.g., attention, attitudes) (Sontag et al., 2019). Additionally, evidence shows that exposure to GHWLs on cigarette packages is associated with increases in cessation-related behaviors such as quit attempts in smokers (Noar et al., 2016a). Besides, compared to cigarettes, ENDS users have more contact with the device itself than the packaging, making the device a promising placement for GHWLs (Mendel et al., 2018). Globally, 40 countries require textual health warnings on ENDS packaging (Institute for Global Tobacco Control, 2020), whereas none of these 40 countries requires ENDS-specific GHWLs. Therefore, it is crucial to provide preliminary evidence about the effectiveness of GHWLs to help guide policy-settings. To date, no clinical trials have explored the effects of placing GHWLs on ENDS devices on users' perception and behavior (e.g., intention to quit or use in the future, craving suppression, puffing behavior, and exposure to nicotine) aimed at reducing the use and risks of ENDS among youth.

Our team has pioneered the use of clinical lab methods to study the effects of GHWLs on emerging tobacco products users' experience and exposure to toxicants. Starting with waterpipe smokers, we tested the effects of applying GHWLs on the waterpipe device during smoking sessions on various subjective (e.g., satisfaction, harm perception, intention to quit) and objective outcomes (e.g., nicotine, puff topography). We found GHWLs reduced smoking satisfaction, puffing behavior compared to no-GHWL control sessions (Maziak et al., 2019a).

As with the waterpipe, ENDS users are usually not exposed much to the packaging, where the current FDA warning is provisioned (US Food and Drug Administration, 2018). Moreover, the current FDA warning is a text-only one, despite the body of evidence showing the superior performance of GHWLs (Noar et al., 2016a; Sontag et al., 2019). Building on this line of work, this proof-of-concept study aims at assessing whether applying GHWLs on the ENDS device could impact important regulatory outcomes (e.g., satisfaction, harm perception, intention to quit or use in the future) and whether it represents a promising policy to curb ENDS use among young people.

Methods

Participants

Twenty-six participants (18-24 years old) were recruited via flyers and word of mouth from the Florida International University (FIU) campus. Participants were consented to enroll in a pilot study using a pre-test/post-test experimental design and attend two lab sessions. Specifically, a within-subject repeated measure design allows for the recruitment of a smaller number of participants in comparison to a between-subject

design and controls individual differences in subjects' overall levels of performance, as each participant acts as their control (Lane, 2003). At the time of this study (early 2019), JUUL was the most popular ENDS among young adults (Herzog & Nielsen, 2019). Therefore, we recruited participants who were current (past month) JUUL users without a self-reported history of chronic health problems, psychiatric conditions, or regular use of prescription medications (other than vitamins or birth control). Those who self-reported current use of more than 5 cigarettes or other tobacco/nicotine products per month in the past year were also excluded. Women were excluded if they were pregnant (tested through urine samples) or breastfeeding.

During each session, participants were seated in a private room with a comfortable reclining chair and were given a choice to watch movies while using JUUL. To ensure safety, the assigned research team member would stop by every 10 minutes to check the participant's status and safety and ensure that all equipment continue properly collecting data during the JUUL use session. As per the study protocol, only one participant was seen at a time, and no one else (i.e., friends or family) was allowed in the room during the study sessions. This study was approved by the FIU Institutional Review Board. Participants completing the two lab sessions were compensated with a total of $125 at the end of the study.

GHWL conditions

We evaluated previous health warning studies and developed a GHWL corresponding to health risks/addiction theme for ENDS (Mendel et al., 2018; Brewer et al., 2019; Sontag et al., 2019). Specifically, the warning used the current FDA modified text "*WARNING: Nicotine in E-cigarettes is Addictive*" associated with a portrait of a

young person being hooked by a fishhook (**Figure 1A**), which has been used for warning campaigns about addiction to tobacco products in the US and other countries (e.g., UK; Byrne, 2007). Different GHWLs for males and females were used, as shown in **Figure 1A**. The GHWLs were printed and taped to both sides of the device. In addition, a JUUL device with a blank surface (without GHWL) was used in the control session.

Procedures

All participants completed two in-person lab sessions during which they vaped their preferred flavor of JUUL *ad libitum* for up to 60 minutes. Since this is a proof-of-concept pilot study that aims to provide first insights on a potentially promising policy of adopting GHWLs on the ENDS device rather than packaging, we compared the current status of the JUUL device (without a GHWL) with the variant of maximum expected effect (with a GHWL). Participants were first assigned to a session without a GHWL. At least 48 hours later, they participated in a session using a JUUL device displaying a GHWL. During the no-GHWL session, participants were asked to bring their own JUUL. For the GHWL session, study participants were provided with an identical JUUL with a GHWL placed on it (as shown in **Figure 1A)**.

The JUUL pod flavors (self-reported preferred flavor) and nicotine content were held constant across the two sessions, but sessions varied by whether the device featured a GHWL or not. Participants were asked to abstain from ENDS and any other tobacco/nicotine use for at least 12 hours prior to study activities (verified by pre-session plasma nicotine levels< 5.0 ng/mL) (Blank et al., 2016). The abstinence period is needed to clear nicotine from prior-to-study uses and ensure that all study measures are influenced mostly by study conditions.

The two sessions were separated by 48 hours washout period (at least) to avoid nicotine's carryover effect. A specialized nurse collected blood samples before and after each session.

Measures

Demographics

Participants completed self-administered questionnaires assessing gender, race/ethnicity, age, and student status.

Other tobacco product use

Participants self-reported the use of any tobacco products by answering the following question ‘Do you regularly use any of the following tobacco/nicotine products: cigarettes, waterpipe, cigar, cigarillos/little cigars, smokeless tobacco, other, and none?’.

JUUL use frequency and patterns

Participants self-reported frequency of JUUL use by responding to the following question: ‘On average, how many JUUL pods do you use per week/month?’ Participants self-reported their JUUL use patterns by responding to the following questions: ‘At what age did you use an e-cigarette for the first time in your life?’, ‘At what age did you use a JUUL e-cigarette for the first time in your life?’, and ‘When did you start using JUUL?’.

Subjective Measures

Computerized self-administered questionnaires (Vehovar & Lozar Manfreda, 2008) were used to collect subjective information during each session:

1) A 10-item Visual Analog Scale (VAS) (Leavens et al., 2018) was used to measure the participants' perception of the product they used (e.g., pleasant, urge to vape, etc.; **Figure 1B**), with items rated on a (0 not at all to 100 extremely) scale. Pointer movement was accomplished by sliding a finger along the tablet's screen to select the score.
2) Two items were used to assess harm perception (Popova & Ling, 2013); 1) In your opinion, how harmful is JUUL to general health; and 2) In your opinion, how harmful is smoking cigarettes for health? The answers to both were rated on a 7-point Likert scale (1 not at all to 7 extremely harmful).
3) Intention to quit was assessed by two items (Jaber et al., 2016); 1) Do you intend to quit using JUUL, with answers options (no; yes in the next month; yes in the next 6 months; yes in the future); and 2) How motivated are you to quit using JUUL in the next month (not motivated; somewhat motivated; very motivated), with answers rated on a (1 not motivated to 3 very motivated) scale.
4) Motivation to use in this study was assessed using two items (Jaber et al., 2016) rated on a (0 not at all to 100 extremely likely) scale. Questions were 1) How interested are you in using the JUUL pod flavor you just used again in the future; and 2) How likely would you use the JUUL pod flavor you just used if it was the only product available in the market?

JUUL puff topography

JUUL puff topography was assessed using a validated topography instrument adapted for JUUL pods (Shihadeh et al., 2005) in both JUUL use sessions. Each JUUL use session was up to 60 minutes. The JUUL device was connected through an adapter to

the puff topography device, which monitored and recorded the participant's puffing behavior throughout the lab session. The puff topography device was developed and validated for ENDS (Spindle et al., 2015; Spindle et al., 2017; Hiler et al., 2017) and adapted for JUUL in our lab (Vargas et al., 2020). The topography software converts signals to airflow (mL/s) and integrates the flow data (topography instrument incorporated and recorded the airflow in terms of graphs), producing measures of total using time, total puff volume, puff duration, inter puff interval (IPI), number of puffs, total volume inhaled and average puff volume (Shihadeh et al., 2005). During the JUUL use sessions, the data and the time for each JUUL user were recorded by an embedded microchip in the topography device, which could be downloaded to a computer immediately or later.

Plasma Nicotine

Plasma nicotine is a standard measure in acute effects lab models for tobacco products (e.g., Maziak et al., 2019a; Maziak et al., 2019b). Blood samples (~10 ml) were drawn via a butterfly needle from the participants' forearm vein before JUUL use session onset and within 10 minutes of its end. Blood samples were centrifuged, plasma was stored at −80°C, and analyzed for nicotine concentration. Our Forensic Chemistry Lab at our university analyzed plasma nicotine samples using the gas chromatography-mass spectrometry (GC-MS) (Jacob et al., 2000), with a limit of detection at 0.2 ng/mL and quantitation at 1.0 ng/mL. The limit of quantitation (LOQ) is defined as the lowest concentration of nicotine that can be precisely determined using the GC-MS method.

Plasma nicotine boost was assessed by subtracting pre-session nicotine level from post-session (Maziak et al., 2019a; Maziak et al., 2019b) and used to compare the amount of exposure to nicotine for each session according to study conditions.

Data analysis

Plasma nicotine concentration values below the limit of quantitation were replaced with 1.0 ng/mL (Ben Taleb et al., 2020). This approach is more conservative than assuming values below the LOQ were zero (Spindle et al., 2015; Ben Taleb et al., 2020). Descriptive statistics for the study sample's characteristics were summarized as mean and standard deviation (SD) or proportions. For the outcomes (subjective measures, puff topography, and plasma nicotine boost), means of the differences (post-pre with 4-time points) were compared by sessions (with or without GHWL) using two-tailed paired samples t-tests. Fisher exact tests were performed to examine the differences in intention to quit by GHWL condition. All analyses were performed in SAS 9.4 version, and results with a p-value< 0.05 were considered statistically significant.

Results

As shown in **Table 1**, study participants (n= 26) had a mean age of 20.9 years± 1.8 years. More than half of the participants were male (62.9%) and Hispanic (84.6%). Most of the participants reported hookah (42.3%) as the first tobacco product they tried, followed by cigarettes (26.9%), JUUL e-cigarette (15.4%), e-cigarettes other than JUUL (7.7%), and cigars (7.7%). The mean age for starting ENDS use was 18.4 years± 2.1 years and for starting JUUL use was 19.5 years± 2.0 years. Fifty percent of the sample reported starting JUUL more than 1 year ago, followed by more than 6 months but less than one year (38.5%) and within the past 6 months (11.5%).

Subjective measures

Subjective measures showed important differences between the two conditions. **Figure 1** depicts mean post-session ratings for three of our subjective measures (VAS and motivation to use), showing a significant reduction in responses signifying pleasure of use, and future motivation to use for JUUL with the GHWL condition ($p< 0.05$ for all). Specifically, means (no-GHWL vs. GHWL) of VAS items for willing to use again (67.73 vs. 49.50; $p= 0.002$), interested to use in the future (64.85 vs. 46.50; $p= 0.005$), product satisfaction (59.96 vs. 42.81; $p= 0.002$), pleasant (42.69 vs. 33.62; $p= 0.05$) and pleasurable to use (58.65 vs. 40.88; $p= 0.001$), enjoy (60.23 vs. 46.73; $p= 0.006$) and like (56.27 vs. 45.27; $p= 0.02$) the product were significantly reduced in GHWL condition compared to no-GHWL condition. Also, participants were less interested in using the same product again (67.15 vs. 48.69; p= 0.007) and less likely to use the product if it was the only product available on the market (69.58 vs. 55.50; $p= 0.03$) in GHWL condition compared to no-GHWL. For the harm perception and intention to quit, no significant differences were found between the two conditions ($p> 0.05$ for all).

JUUL puff topography

Two participants were missing topography data for the no-GHWL session due to software technical issues. Though not significant, for some of the puffing parameters (puffing time, number of puffs, total volume), there was a consistent tendency towards lower values in the GHWL condition compared to control (**Table 2**).

Plasma nicotine

Eighteen participants were included in the plasma nicotine analysis. Eight participants were excluded from the analysis: three participants were not nicotine

abstinent for the no-GHWL pre-session, and our chemistry lab was unable to perform nicotine analysis for five participants that completed the GHWL session due to a complete university shutdown in response to the COVID-19 pandemic. There were 16 and 15 measurements below the limit of quantitation in the no-GHWL and GHWL pre-session, respectively. The values were replaced with 1.0 ng/mL. The mean (SD) of plasma nicotine boost level was lower in the GHWL condition (5.35± 6.41 ng/mL) compared to control (6.95± 9.26 ng/mL), but the difference was not statistically significant (p= 0.073). This demonstrated that changes in plasma nicotine concentration across time did not depend on the GHWL condition.

Discussion

This clinical lab study is the first to provide a proof-of-concept that placing a GHWL on the ENDS device can be effective in reducing users' positive experience (e.g., product enjoyment, willingness to use, etc.) and motivation to use in the future. Trends toward reduced puffing behavior and nicotine boost were also noted among those exposed to the GHWL, highlighting a consistent trend towards less intensive and enjoyable use behavior as a result of GHWL. These findings support the notion that placing GHWL on the ENDS device can be an effective and promising strategy to reduce ENDS appeal and use for young people.

By placing the GHWL on the ENDS device, we could provide the first evidence of the potential of this approach to reduce positive use experience, puffing behavior, and motivation to use in the future. Only one study so far has examined the effects of graphic versus text-only health warnings on ENDS devices (Brewer et al., 2019).

However, this study investigated the effects of GHWLs through online viewing of GHWLs and tested communication and perceived harm outcomes, while our study is the first clinical study to test the effects of GHWLs on the device on use experience and behavior in real-time; i.e., during actual use.

Our observed diminished subjective experience and future motivation to use the same product in the GHWL condition are in line with the cigarette literature (Schneider et al., 2012; Blanton et al., 2014; Evans et al., 2015). For example, a randomized controlled trial demonstrated that GHWLs on cigarette packaging had negative effects on adult smokers' subjective experience (such as increased fear, worries, uncomfortableness, or disgust) (Schneider et al., 2012). Also, an online experimental study based on a US young adult population showed that GHWLs had the potential to lower the smoking willingness and intentions (Blanton et al., 2014).

In addition, when we planned the study, we hypothesized that in the GHWL condition, participants would have reduced puffing behavior and thus reduced exposure to nicotine. While we observed a consistent decrease in puffing behavior (e.g., total inhaled volume, number of puffs, and puffing time) and nicotine boost during GHWL condition compared to no-GHWL, these results were not statistically significant. One likely explanation of lower sensitivity of puffing behavior and nicotine uptake to the GHWL compared to other outcomes (e.g., satisfaction) may lie in the predominance of nicotine dependence over other factors (e.g., study conditions) in this acute lab model. Accordingly, users adapt their puffing behavior to obtain the same dose of nicotine they are used to regardless of study conditions (Maziak et al., 2019b; Ben Taleb et al., 2020; Vargas et al, 2020). The dissociation of the responses to GHWLs in this acute model,

however, does not preclude their long-term potential effectiveness by increasing the negative affect associated with the behavior (Durkin et al., 2015; Noar et al., 2016b). Future studies can help elucidate the long-term impact of repeated exposure to GHWLs, and how they affect different subjective and objective outcomes.

As mentioned earlier, GHWLs for ENDS may lead to unintended consequences, leading to more cigarette smoking and discouraging adult smokers from using the ENDS devices for cessation purposes (Pacek et al., 2019). While not in our study, the concern was addressed by a recent study showing that ENDS GHWLs had no effect on encouraging cigarette smoking (Brewer et al., 2019). Moreover, there is limited evidence about ENDS effectiveness as a cessation or harm reduction tool for adults (e.g., Hajek et al., 2019), especially in real-world settings. Real-world perspective studies with nationwide samples in the US (e.g., the Population Assessment of Tobacco and Health, PATH) have shown that dual-use remains the most common trajectory of ENDS use in the society (Watkins et al., 2018) and that former cigarette smokers using ENDS are more likely to relapse to cigarette smoking compared to those who did not use ENDS (Dai & Leventhal, 2019b; Everard et al., 2020). Therefore, until additional policies that can tailor ENDS products for smoking cessation are available, the combination of a highly addictive ENDS that is marketed and popular among youth is not in the best interest of public health.

This is a pilot study with limited scope, where we used only one type of GHWL message. It was also limited in its assessment of the effect of GHWL, for example, it did not address the effects of GHWLs on bystanders who will be exposed to such GHWL but

not through personal use. Such a prospect is likely to enhance the total population effect of applying GHWLs on ENDS devices, particularly given that peer influence is important for ENDS use (Leavens et al., 2019) and that conversations sparked by GHWLs are one of how they impact quit attempts (Morgan et al., 2018). Moreover, participants followed a fixed order of sessions to avoid any carryover effect (from GHWL to no GHWL), rather than randomized to the study conditions. We believe that the setup is ideal for this study to avoid contamination in responses to the study conditions by prior exposure. Furthermore, GHWLs will likely affect nonusers in terms of deterring initiation. However, since our proposed lab study involves the use of potentially harmful products (i.e., ENDS), we could not include nonusers. Future studies with a larger sample size perhaps will be needed to assess the effect of GHWLs on these unintended consequences (e.g., smoking initiation, discouraging smokers from quitting cigarette), and to test the GHWLs on other ENDS devices with different themes (e.g., ENDS harm compared with cigarettes), shapes, sizes, and attributes (e.g., heating power, disposable vs. refillable).

Conclusions

Notwithstanding, our study provides support for the effectiveness of GHWL on the device in the way that it is likely to be encountered by users (during use) and on outcomes that have important implications for regulatory efforts to limit ENDS use among young people. This approach is consistent with the differences in packaging and use patterns between ENDS and cigarettes, where ENDS users have extended contact with the device itself but limited contact with the packaging. Such line of work will benefit from the accumulating evidence about ENDS harms, which will expand the range of ENDS health warnings beyond the effect of nicotine and addiction as it is currently

adopted by the FDA. Accordingly, new textual warnings and their accompanying graphical images need to be developed and tested. Our lab-based approach and pilot data can provide a good model for evaluating new GHWLs for ENDS. Given the alarming pace of the ENDS epidemic, particularly among young people in the US, we believe that our pilot findings are timely needed to advance potentially effective avenues for research and policy to reduce ENDS use among youth.

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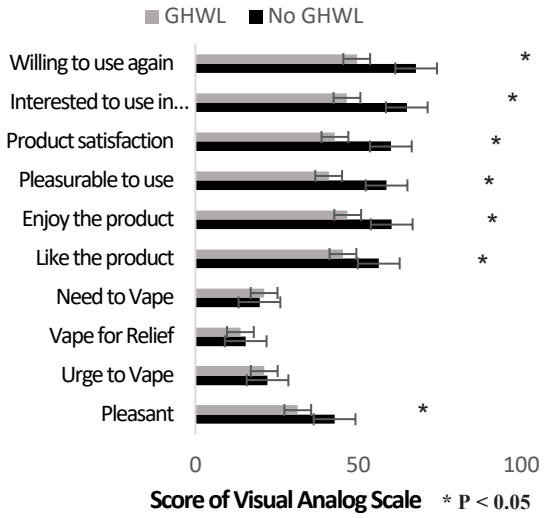
Tables and Figures

Figure 1: Illustration of JUUL devices with GHWLs (the first picture for male and the second picture for female; panel A) and no-GHWL (the third picture; panel A) and means (±SEM) for post-session of participant's response to 2 of the subjective measures: Subjective measures presented as Visual Analog Scale (VAS) (panel B) and Motivation to Use (panel C) (n=26).

A

B



C

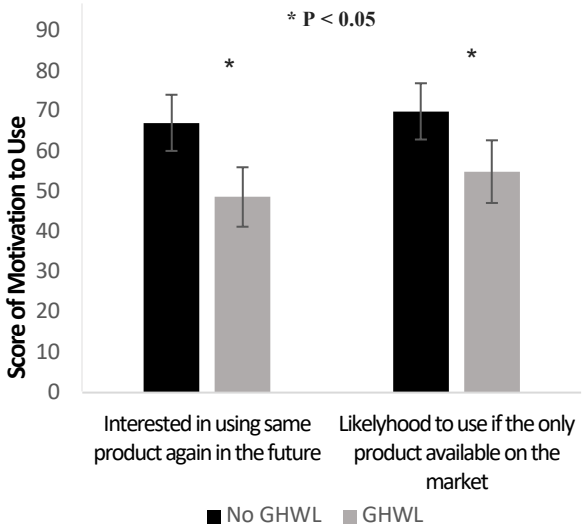


Table 1: Baseline characteristics for the overall sample (n=26).

Variables	Overall Sample
Gender (male) (%)	69.2
Race/Ethnicity (%)	
Asian/Pacific Islander	3.9
Black	7.7
Caucasian/White	3.9
Hispanic/Latino	84.6
Other tobacco use (%)†	
Cigarette	73.1
Other E-cigarettes	15.4
Hookah	3.8
None	7.7
When started JUUL (%)	
Within the past 6 months	3 (11.5)
More than 6 months but less than one year	10 (38.5)
More than 1 year ago	13 (50.0)
Student status (%)	92.3
Favorite Flavors (%)	
Mint	17 (65.4)
Mango	6 (23.1)
Others	3 (11.5)
Which product first tried (%)	
JUUL	15.4
Other E-cigs	7.7
Cigarettes	26.9
Cigars	7.7
Hookah	42.3
Age (in years) *	20.9 (1.8)
Age first E-cig used (in years) *	18.4 (2.1)
Age first JUUL used (in years) *	19.5 (2.0)
JUUL pods per week *	2.5 (1.6)

* Data presented as mean (SD).

† Less than five times/months.

Table 2: JUUL puff topography measures by study conditions (n=26).

Topography parameters	No GHWL (n=24) *		GHWL (n=26)		P-value
	Mean	SD	Mean	SD	
Vaping time (min)	48:50	13:13	43:20	13:45	0.13
Puffing time (min)	1:59	1:23	1:40	1:12	0.32
Puff duration (s)	2.9	1.4	3.0	1.3	0.47
Inter-puff interval (s)	90.4	54.8	107.2	84.9	0.22
Number of puffs	41.9	27.5	34.0	20.8	0.20
Total volume (L)	1.5	1.1	1.2	1.2	0.36
Puff volume (ml)	37.6	22.1	38.5	22.6	0.77
Max puff volume (ml)	66.9	41.1	63.4	39.9	0.59

* Two participants were missing data only in the no-GHWL group due to software technical issues.

Abbreviation: GHWL, graphic health warning label

Note: "Vaping time" refers to the time participants initiate using JUUL until they finish; "Puffing time" refers to the total time of participants in vaping during the session; "Puff durations" refers to each period of puffing; "Inter-puff intervals" was calculated by subtraction between duration of the puff by the time of the previous puff; "Numbers of puffs" means the numbers of a participant puff during the session; "Total volume" refers to the sum of puff volume during the session; "Puff volume" means each time of puff volume during the session; "Max puff volume" refers to the maximum volume of puff during the session.

CONCLUSIONS

The purpose of this dissertation was to provide a dynamic picture of harm perception influences on ENDS use at the population level in a real-world setting and investigate how the harm perception of ENDS changed over time and test a promising strategy to communicate and affect risk/harm perception among US young users. The first study showed that 17.1% of the adolescents and 25.5% of the young adults initiated ENDS use across four waves. The perception of ENDS as a reduced or low-harm product strongly predicted ENDS initiation in the subsequent waves among US young people. Additionally, adolescents and young adults who experimented with other tobacco products or alcohol and lived with anyone who used tobacco were at increased risks of ENDS initiation. These results highlight the importance of harm perception for ENDS initiation. Characterizing the role of harm perception in ENDS initiation in a real-world setting can help inform specific risk communication strategies to reduce unwarranted ENDS uptakes among young people.

We further demonstrated in our second study that US adolescents have become more aware of ENDS harms over time. While ENDS-related harm perception had generally increased, this did not appear to be equally experienced across all adolescents (i.e., less robust among those who were male, who did not have positive tobacco-related attitudes, who had smoke-free home rules, who ever used ENDS or alcohol, and who lived with someone used tobacco), potentially highlighting the significance of at-risk groups and targets for intervention. This study helped identify individuals at risk of ENDS initiation because of their favorable ENDS harm perception profile and guided the development of ENDS risk communication interventions for young people.

Finally, the last study tested a promising strategy through risk communication to curb ENDS use among young users. Specifically, an experimental study design was used to evaluate the effect of placing GHWLs on ENDS devices on users' experience, puffing patterns, harm perception, nicotine exposure, and intention to quit or use in the future. This was the first clinical lab study to provide a proof-of-concept that placing GHWLs on ENDS devices effectively reduce users' positive experience (e.g., product enjoyment, willingness to use, etc.) and motivation to use in the future. These findings supported the notion that placing GHWLs on the ENDS devices can be a promising and effective strategy to reduce ENDS appeal and use among young people.

Collectively, the findings from the four waves of the PATH study on the evolution of harm perception and its effects on ENDS use among US young people in the real-world setting underscore the importance of ENDS harm perception and the central role of risk communication strategies that need to target those at particular risk of unwarranted ENDS use. Additionally, findings from this study also emphasize the demand for stricter and more effective tobacco regulatory policies to deter the ENDS epidemic among young people. Future longitudinal and cohort studies are continuously needed to monitor the harm perception of tobacco products on ENDS use and investigate the long-term consequences of ENDS use to eliminate ENDS use among young people.

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